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(54) Title: COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

(57) Abstract

Disclosed are compounds which bind VLA-4. Certain of these compounds also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compounds are useful in the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compounds can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis.

COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benfit of U.S. Provisional Application No. 60/___,___, which was converted pursuant to 37 C.F.R. §1.53(c)(2)(i) from U.S. Patent Application No. 08/904,416, filed July 31, 1997, the disclosure of which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to compounds which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4.

References

The following publications, patents and patent applications are cited in this application as superscript numbers:

[1] Hemler and Takada, *European Patent Application Publication No.* 330,506, published August 30, 1989

[2] Elices, et al., *Cell*, 60:577-584 (1990)

[3] Springer, *Nature*, 346:425-434 (1990)

[4] Osborn, *Cell*, 62:3-6 (1990)

[5] Vedder, et al., *Surgery*, 106:509 (1989)

[6] Pretolani, et al., *J. Exp. Med.*, 180:795 (1994)

[7] Abraham, et al., *J. Clin. Invest.*, 93:776 (1994)

[8] Mulligan, et al., *J. Immunology*, 150:2407 (1993)

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[19] van Dinther-Janssen, et al., *Annals. Rheumatic Dis.*, 52:672 (1993)

[20] Elices, et al., *J. Clin. Invest.*, 93:405 (1994)

[21] Postigo, et al., *J. Clin. Invest.*, 89:1445 (1991)

[22] Paul, et al., *Transpl. Proceed.*, 25:813 (1993)

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[25] Schadendorf, et al., *J. Path.*, 170:429 (1993)

[26] Bao, et al., *Diff.*, 52:239 (1993)

[27] Lauri, et al., *British J. Cancer*, 68:862 (1993)

[28] Kawaguchi, et al., *Japanese J. Cancer Res.*, 83:1304 (1992)

[29] Kogan, et al., *U.S. Patent No. 5,510,332*, issued April 23, 1996

[30] International Patent Appl. Publication No. WO 96/01644

All of the above publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

<u>State of the Art</u>

VLA-4 (also referred to as $\alpha_4\beta_1$ integrin and CD49d/CD29), first identified by Hemler and Takada[1] is a member of the β1 integrin family of cell surface receptors, each of which comprises two subunits, an α chain and a β chain. VLA-4 contains an α4 chain and a β1 chain. There are at least nine β1 integrins, all sharing the same β1 chain and each having a distinct α chain. These nine receptors all bind a different complement of the various cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4, for example, binds to fibronectin. VLA-4 also binds non-matrix molecules that are expressed by endothelial and other cells. These non-matrix molecules include VCAM-1, which is expressed on cytokine-activated human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-4 are responsible for the fibronectin and VCAM-1 binding activities and each activity has been shown to be inhibited independently.[2]

Intercellular adhesion mediated by VLA-4 and other cell surface receptors is associated with a number of inflammatory responses. At the site of an injury or other inflammatory stimulus, activated vascular endothelial cells express molecules that are adhesive for leukocytes. The mechanics of leukocyte adhesion to endothelial cells involves, in part, the recognition and binding of cell surface receptors on leukocytes to the corresponding cell surface molecules on endothelial cells. Once bound, the leukocytes migrate across the blood vessel wall to enter the injured site and release

chemical mediators to combat infection. For reviews of adhesion receptors of the immune system, *see*, for example, Springer[3] and Osborn[4].

Inflammatory brain disorders, such as experimental autoimmune encephalomyelitis (EAE), multiple sclerosis (MS) and meningitis, are examples of central nervous system disorders in which the endothelium/leukocyte adhesion mechanism results in destruction to otherwise healthy brain tissue. Large numbers of leukocytes migrate across the blood brain barrier (BBB) in subjects with these inflammatory diseases. The leukocytes release toxic mediators that cause extensive tissue damage resulting in impaired nerve conduction and paralysis.

In other organ systems, tissue damage also occurs via an adhesion mechanism resulting in migration or activation of leukocytes. For example, it has been shown that the initial insult following myocardial ischemia to heart tissue can be further complicated by leukocyte entry to the injured tissue causing still further insult (Vedder et al.[5]). Other inflammatory conditions mediated by an adhesion mechanism include, by way of example, asthma[6-8], Alzheimer's disease, atherosclerosis[9-10], AIDS dementia[11], diabetes[12-14] (including acute juvenile onset diabetis), inflammatory bowel disease[15] (including ulcerative colitis and Crohn's disease), multiple sclerosis[16-17], rheumatoid arthritis[18-21], tissue transplantation[22], tumor metastasis[23-28], meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

In view of the above, assays for determining the VLA-4 level in a biological sample containing VLA-4 would be useful, for example, to diagnosis VLA-4 mediated conditions. Additionally, despite these advances in the understanding of leukocyte adhesion, the art has only recently addressed the use of inhibitors of adhesion in the treatment of inflammatory brain diseases and other inflammatory conditions[29,30]. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

This invention provides compounds which bind to VLA-4. Such compounds can be used, for example, to assay for the presence of VLA-4 in a sample and, in pharmaceutical compositions, to inhibit cellular adhesion mediated by VLA-4, for example, binding of VCAM-1 to VLA-4. The compounds of this invention have a binding affinity to VLA-4 as expressed by an IC_{50} of about 15 μM or less (as measured using the procesure shown in Example 46 below) which compounds are defined by formula I below:

$$\begin{array}{c} \quad\quad\quad\quad\quad\quad\quad\quad\quad R^3 \quad\quad O \\ \quad\quad\quad\quad\quad\quad\quad\quad\quad | \quad\quad\quad \| \\ R^1\text{-}SO_2\text{-}N(R^2)\text{-}C\text{-}Q\text{-}CH\text{-}C\text{-}OH \\ \quad\quad\quad\quad\quad\quad\quad\quad | \quad\quad | \\ \quad\quad\quad\quad\quad\quad\quad\quad H \quad\ R^5 \end{array} \qquad \text{I}$$

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, and substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form an unsaturated heterocyclic group or a unsaturated substituted heterocyclic group;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic,

with the further provisos that:

A. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is $-O-Z-NR^8R^{8'}$ or $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, and substituted heterocyclic, and R^8 and $R^{8'}$ can be joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

B. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is $-NR^{12}C(Z')NR^8R^{8'}$ or $-NR^{12}C(Z)R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{12}, R^{12} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is sustituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, or substituted heterocyclic or R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated

heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, and R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino, substituted heterocycles,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,

x is an integer of from 1 to 4;

C. R^5 is not -ALK-X' where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group ($-CH_2-$) to the carbon atom to which it is attached; X' is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroaryloxycarbonyl, substituted heteroaryloxycarbonyl, heterocyclyloxycarbonyl, substituted heterocyclyloxycarbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocarbonylamino, guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, $-OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, $-OS(O)_2$-cycloalkyl, $-OS(O)_2$-substituted cycloalkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-cycloalkyl, $-NRS(O)_2$-substituted cycloalkyl, -$NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-cycloalkyl, $-NRS(O)_2$-NR-substituted cycloalkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, -

NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, -S(O)$_2$-alkyl, -S(O)$_2$-substituted alkyl, -S(O)$_2$-aryl, -S(O)$_2$-substituted aryl, -S(O)$_2$-substituted heteroaryl, -S(O)$_2$-substituted heteroaryl, -S(O)$_2$-heterocyclic, -S(O)$_2$-substituted heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-(substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl, substituted heterocyclic)amino;

D. R^5 is not -$(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is a substituent selected from the group consisting of:

(a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino,

oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and $-COOR^{23}$ where R^{23} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic,

(c) aryl and heteroaryl;

(d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is

selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and alkyl/substituted alkyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted alkyl, -SO$_2$-alkenyl, -SO$_2$-substituted alkenyl, -SO$_2$-cycloalkyl, -SO$_2$-substituted cycloalkyl, -SO$_2$-

aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(e) -alkoxy-NR″R″ wherein each R″ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when each R″ is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted arylamino), mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono-

and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic; substituted heterocyclic, and substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and alkyl/substituted alkyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl;

(f) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(g) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic; (h) -O-heterocyclic and -O-substituted heterocyclic;

(i) tetrazolyl;

(j) -NR-SO_2-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(k) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

(l) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR″R″, unsaturated heterocyclyl,

alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(m) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(n) -C(O)NR'''R''' where each R''' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R''' is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

(o) $-NR^{22}C(O)-R^{18}$ where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(p) $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl or $-SO_2$-alkyl;

(q) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl,

substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic:

(r) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) -aminocarbonyl-(N-formylheterocyclcyl); and

(t) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl, and

E. When R^3 is other than H, R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy,

heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof

and still further with the following provisos excluding the following compounds

A. when R^1 and R^2 are joined together with the SO_2 and nitrogen atom to which they are attached respectively to form a benzoisothiazolone heterocyclic ring, R^3 is hydrogen, and Q is -C(O)NH-, then R^5 is not benzyl; and

B. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 is hydrogen, Q is $-C(O)NCH_3-$, then R^5 is not benzyl.

In another embodiment, the compounds of this invention can also be provided as prodrugs which convert (e.g., hydrolyze, metabolize, etc.) *in vivo* to a compound of formula I above. In a preferred example of such an embodiment, the carboxylic acid in the compound of formula I is modified into a group which, *in vivo*, will convert to the carboxylic acid (including salts thereof). In a particularly preferred embodiment, such prodrugs are represented by compounds of formula IA:

$$\begin{array}{l} \qquad\qquad\qquad\quad\; R^3 \qquad\;\; O \\ \qquad\qquad\qquad\quad\;\; | \qquad\quad\; \| \\ R^1\text{-}SO_2\text{-}N(R^2)\text{-}C\text{-}Q\text{-}CH\text{-}C\text{-}R^6 \\ \qquad\qquad\qquad\quad\;\; | \qquad | \\ \qquad\qquad\qquad\quad\; H \quad\; R^5 \end{array} \qquad \text{IA}$$

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form an unsaturated heterocyclic group or a unsaturated substituted heterocyclic group;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where p is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z''$ where Z" is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur;

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic

with the further provisos that:

A. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-O-Z-NR^8R^{8'}$ and $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

B. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{12}C(Z')NR^8R^{8'}$ and $-NR^{12}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{12}, R^{12} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is sustituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, substituted heterocyclic or R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, and R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycle other than morpholino and thiomorpholino,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,

x is an integer of from 1 to 4;

C. R^5 is not -ALK-X' where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group ($-CH_2-$) to the carbon atom to which it is attached; X' is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroaryloxycarbonyl, substituted heteroaryloxycarbonyl, heterocyclyloxycarbonyl, substituted heterocyclyloxycarbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocarbonylamino,

guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-cycloalkyl, $-OS(O)_2$-substituted cycloalkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-cycloalkyl, $-NRS(O)_2$-substituted cycloalkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-cycloalkyl, $-NRS(O)_2$-NR-substituted cycloalkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-(substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl, substituted heterocyclic)amino; and

D. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is a substituent selected from the group consisting of:

(a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl,

amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-

substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and $-COOR^{23}$ where R^{23} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic,

(c) aryl and heteroaryl;

(d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic or substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl,

-$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl;

(e) -alkoxy-NR″R″ wherein each R″ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when each R″ is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy,

heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(f) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(g) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic;

(h) -O-heterocyclic and -O-substituted heterocyclic;

(i) tetrazolyl;

(j) -NR-SO_2-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(k) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

(l) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR"R", unsaturated heterocyclic, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(m) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(n) -C(O)NR'''R''' where each R''' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R''' is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino,

N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic or substituted heterocyclic;

(o) $-NR^{22}C(O)-R^{18}$ where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(p) $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl or $-SO_2$-alkyl;

(q) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic:

(r) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) -aminocarbonyl-(N-formylheterocylcyl); and

(t) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl,

E. When R^3 is other than H, R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic

with the proviso that when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -OSO_2-NRR, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl

groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof

with the following provisos

A. when R^1 is *o*-carboxymethylphenyl, R^2 is hydrogen, R^3 is hydrogen or methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

B. when R^1 and R^2 are joined to form a benzoisothiazolone heterocyclic ring, R^3 is hydrogen or methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

C. when R^1 is *p*-methylphenyl, R^2 is hydrogen, R^5 is benzyl or *p*-hydroxybenzyl, R^3 is -$(CH_2)_s$C(O)O-*t*-butyl where *s* is 1 or 2, Q is -C(O)NH-, then R^6 is not -O-*t*-butyl;

D. when R^1 is *p*-methylphenyl, R^2 is methyl, R^5 is benzyl, R^3 is -$CH(\phi)_2$, Q is -C(O)NH-, then R^6 is not -O-benzyl;

E. when R^1 is *p*-methylphenyl, R^2 is methyl, R^5 is methyl, R^3 is -hydroxymethyl, Q is -C(O)NH-, then R^6 is not -O-methyl; and

F. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 is methyl or *t*-butyl, R^5 is *p*-hydroxybenzyl, Q is -C(O)NH-, then R^6 is not -O-*t*-butyl.

Preferably, in the compounds of formula I and IA above, R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl. Even more preferably R^1 is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-(CH_3C(O)NH-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-

bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

Preferably, in the compounds of formula I and IA above, R^2 is hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-ϕ.

In one embodiment, R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 are joined to form a heterocyclic group or substituted heterocyclic group. Preferred heterocyclic and substituted heterocyclic groups include those having from 5 to 7 ring atoms having 2 to 3 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur which ring is optionally fused to another ring such as a phenyl or cyclohexyl ring to provide for a fused ring heterocycle of from 10 to 14 ring atoms having 2 to 4 heteroatoms in the ring selected from the group consisting of nitrogen, oxygen and sulfur. Specifically preferred R^1/R^2 joined groups include, by way of example, benzisothiazolonyl (saccharin-2-yl).

Preferably, in the compounds of formula I and IA above, R^3 includes all of the isomers arising by substitution with methyl, phenyl, benzyl, diphenylmethyl, -CH_2CH_2-COOH, -CH_2-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH_2O-benzyl and hydroxymethyl.

Q is preferably -C(O)NH- or -C(S)NH-.

R^5 is preferably selected from the group consisting of all possible isomers arising by substitution with the following groups: benzyl, (*N*-benzylimidazol-4-yl)methyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, 4-[2-

(pyridin-2-yl)ethynyl]benzyl, 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-iodobenzyl, 4-cyanobenzyl, 4-(2-bromobenzamido)benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, and 4-hydroxybenzyl.

In the compounds of formula IA, R^6 is preferably 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2-α-*iso*-propyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, $-NH_2$, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHCH_2CH_2COOCH_2CH_3$, $-NHSO_2$-*p*-CH_3-ϕ, $-NHOR^8$ where R^8 is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, -OCH_2-$OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR″C(O)-R′ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or $-CH_2C(O)OCH_2CH_3$.

Preferred compounds within the scope of formula I and IA above include by way of example:

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-phenylalanine

N-(toluene-4-sulfonyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)glycyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)-L-alanyl-L-phenylalanine

N-(saccharin-2-yl)-L-alanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-phenylalanyl-D,L-phenylalanine

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(3-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(4-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-L-β-(2-pyridyl)alanine

N-(toluene-4-sulfonyl)-D,L-phenylsarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-aspartyl-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinolin-3-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(pyridin-2-yl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(3-hydroxyphenyl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-(iodo)phenylalanine

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-cyanophenylalanine

N-(toluene-4-sulfonyl)-L-*tert*-butylglycyl-L-phenylalanine

N-(saccharin-2-yl)-D,L-alaninyl-L-4-(isonicotinamido)phenylalanine methyl ester

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

This invention also provides methods for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of formula I or IA above under conditions wherein said compound binds to VLA-4.

Certain of the compounds of formula I and IA above are also useful in reducing VLA-4 mediated inflammation *in vivo*.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of formula I or IA above with the exception that R^3 and R^5 are derived from L-amino acids or other similarly configured starting materials. Alternatively, racemic mixtures can be used.

The pharmaceutical compositions may be used to treat VLA-4 mediated disease conditions. Such disease conditions include, by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetis), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

Accordingly, this invention also provides methods for the treatment of an inflammatory disease in a patient mediated by VLA-4 which methods comprise administering to the patient the pharmaceutical compositions described above.

Preferred compounds of formula I and IA above include those set forth in Table I below:

Table I

$$
\begin{array}{l}
\qquad\qquad\qquad\quad R^3 \qquad\quad O \\
\qquad\qquad\qquad\quad | \qquad\quad\;\; \| \\
R^1\text{-}SO_2\text{-}N(R^2)\text{-}C\text{-}Q\text{-}CH\text{-}C\text{-}R^{6'} \\
\qquad\qquad\qquad\quad | \qquad | \\
\qquad\qquad\qquad\quad H \qquad R^5
\end{array}
$$

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7- R^7
p-CH_3-ϕ-	R^2/R^3 = L-2,3-dihydroindol-2-yl		-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	R^2/R^3 = L-1,2,3,4-tetrahydro-quinolin-2-yl		-CH_2-ϕ	-OH	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7- R^7
p-CH_3-ϕ-	H	H	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	-CH_3	H	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	H	CH_3 (L isomer)	-CH_2-ϕ	-OH	H
o-methoxy-carbonyl-ϕ-	H	H	-CH_2-ϕ	-OH	H
o-methoxy-carbonyl-ϕ-	H	-CH_3 (L isomer)	-CH_2-ϕ	-OH	H
saccharin-2-yl		CH_3 (L isomer)	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	H	ϕ-	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	-CH_3	benzyl (L-isomer)	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	H	L -CH(ϕ)$_2$	-CH_2-ϕ	-OH	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7-R^7
p-CH_3-ϕ-	-CH_3	L -CH(ϕ)$_2$	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	-CH_3	H	1-N-benzylimidazol-4-yl-CH_2-	-OH	H
p-CH_3-ϕ-	-CH_3	H	3-pyridyl-CH_2-	-OH	H
p-CH_3-ϕ-	-CH_3	H	4-pyridyl-CH_2-	-OH	H
p-CH_3-ϕ-	-CH_3	H	2-pyridyl-CH_2-	-OH	H
p-CH_3-ϕ-	-CH_3	-ϕ (L isomer)	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	H	HOOCCH_2- (L isomer)	-CH_2-ϕ	-OH	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7-R^7
p-CH_3-ϕ-	R^2/R^3 = L-1,2,3,4-tetrahydro-quinolin-2-yl		-CH_2-ϕ	-O-CH_2-ϕ	H
p-CH_3-ϕ-	R^2/R^3 = L-2,3-dihydroindol-2-yl		-CH_2-ϕ	-O-CH_2-ϕ	H
p-CH_3-ϕ-	H	-CH_3 (L isomer)	-CH_2-ϕ	-O-CH_2-ϕ	H
p-CH_3-ϕ-	-CH_3	H	-CH_2-ϕ	-O-CH_2-ϕ	H
p-CH_3-ϕ-	H	-ϕ (L-isomer)	-CH_2-ϕ	-OCH_2CH_3	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = $-C(O)NR^7-$ R^7
p-CH_3-ϕ-	$-CH_3$	$-CH_2O-$ benzyl (L-isomer)	$-CH_2$-ϕ	$-OCH_2CH_3$	H
p-CH_3-ϕ-	$-CH_3$	$-CH_2OH$ (L-isomer)	$-CH_2$-ϕ	$-OCH_2CH_3$	H
p-CH_3-ϕ-	H	-CH(ϕ)$_2$ (L-isomer)	$-CH_2$-ϕ	-O-CH_2-ϕ	H
p-CH_3-ϕ-	ϕ	H	$-CH_2$-ϕ	OH	H
p-CH_3-ϕ-	$-CH_3$	-ϕ (L isomer)	$-CH_2$-ϕ	$-OCH_2CH_3$	H
p-CH_3-ϕ-	$-CH_3$	H	1-N-benzylimidazol-4-yl-CH_2-	$-OCH_3$	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7-R^7
p-CH_3-φ-	-CH_3	-CH_2OH (L isomer)	1-N-benzylimidazol-4-yl-CH_2-	-OCH_3	H
p-CH_3-φ-	H	φ (L isomer)	-CH_2-φ	-OCH_2φ	H
p-CH_3-φ-	-CH_3	φ (L isomer)	-CH_2-φ	-OCH_2φ	H
p-CH_3-φ-	-CH_2φ	H	-CH_2-φ	-OCH_3	H
p-CH_3-φ-	-CH_2φ	H	-CH_2-φ	-OH	H
p-CH_3-φ-	-CH_3	H	*p*-[-C≡C-(2-pyridyl)]-benzyl-	-OH	H
p-CH_3-φ-	-CH_3	H	*p*-[-C≡C-(*m*-hydroxyphenyl)]-benzyl-	-OH	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7-R^7
p-CH_3-ϕ-	-CH_3	H	*p*-iodobenzyl-	-OH	H
p-CH_3-ϕ-	-$(CH_2)_2$-2-thienyl	H	-CH_2-ϕ	-OCH_3	H
p-CH_3-ϕ-	-$(CH_2)_2$-2-thienyl	H	-CH_2-ϕ	-OH	H
ϕ-CH_2-	-CH_3	-CH_2OH (L isomer)	1-N-benzylimidazol-4-yl-CH_2-	-OCH_3	H
p-CH_3-ϕ-	-CH_2CH_2ϕ	H	1-N-benzylimidazol-4-yl-CH_2-	-OCH_3	H
p-CH_3-ϕ-	-CH_2CH_2ϕ	H	-CH_2-ϕ	-OH	H
p-CH_3-ϕ-	-CH_3	H	*p*-cyanobenzyl-	-OH	H

R^1	R^2	R^3	R^5	$R^{6'}$	Q = $-C(O)NR^7-R^7$
p-CH_3-ϕ-	H	*tert*-butyl	$-CH_2$-ϕ	-OH	H
R^1/R^2 = benzisothiazolone		$-CH_3$	*p*-(pyridin-4-yl-C(O)NH)benzyl-	$-OCH_3$	H

DETAILED DESCRIPTION OF THE INVENTION

As above, this invention relates to compounds which inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. However, prior to describing this invention in further detail, the following terms will first be defined.

Definitions

As used herein, "alkyl" refers to alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl and the like.

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkyl amidino,thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxylaryl, substituted aryloxyaryl, cyano, halogen, hydroxyl, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted

cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl,
$-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl.

"Alkoxy" refers to the group "alkyl-O-" which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-".

"Acyl" refers to the groups H-C(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, alkenyl-C(O)-, substituted alkenyl-C(O)-, alkynyl-C(O)-, substituted alkynyl-C(O)- cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, substituted aryl-C(O)-, heteroaryl-C(O)-, substituted heteroaryl-C(O), heterocyclic-C(O)-, and substituted heterocyclic-C(O)- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Thiocarbonylamino" refers to the group -C(S)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring wherein alkyl, substituted alkyl, alkenyl,

substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O- wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Alkenyl" refers to alkenyl group preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation.

"Substituted alkenyl" refers to alkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl,

thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkenyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkenyl/substituted alkenyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl.

"Alkynyl" refers to alkynyl group preferably having from 2 to 10 carbon atoms and more preferably 3 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation.

"Substituted alkynyl" refers to alkynyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl,

-NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkynyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkynyl/substituted alkynyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted alkyl, -SO$_2$-alkenyl, -SO$_2$-substituted alkenyl, -SO$_2$-cycloalkyl, -SO$_2$-substituted cycloalkyl, -SO$_2$-aryl, -SO$_2$-substituted aryl, -SO$_2$-heteroaryl, -SO$_2$-substituted heteroaryl, -SO$_2$-heterocyclic, -SO$_2$-substituted heterocyclic or -SO$_2$NRR, where R is hydrogen or alkyl.

"Amidino" refers to the group H$_2$NC(=NH)- and the term "alkylamidino" refers to compounds having 1 to 3 alkyl groups (e.g., alkylHNC(=NH)-).

"Thioamidino" refers to the group RSC(=NH)- where R is hydrogen or alkyl.

"Aminoacyl" refers to the groups -NRC(O)alkyl, -NRC(O)substituted alkyl, -NRC(O)cycloalkyl, -NRC(O)substituted cycloalkyl, -NRC(O)alkenyl, -NRC(O)substituted alkenyl, -NRC(O)alkynyl, -NRC(O)substituted alkynyl, -NRC(O)aryl, -NRC(O)substituted aryl, -NRC(O)heteroaryl, -NRC(O)substituted heteroaryl, -NRC(O)heterocyclic, and -NRC(O)substituted heterocyclic

where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonyloxy" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-alkenyl, -NRC(O)O-substituted alkenyl, -NRC(O)O-alkynyl, -NRC(O)O-substituted alkynyl, -NRC(O)O-cycloalkyl, -NRC(O)O-substituted cycloalkyl, -NRC(O)O-aryl, -NRC(O)O-substituted aryl, -NRC(O)O-heteroaryl, -NRC(O)O-substituted heteroaryl, -NRC(O)O-heterocyclic, and -NRC(O)O-substituted heterocyclic where R is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxycarbonylamino" refers to the groups -OC(O)NH_2, -OC(O)NRR, -OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-alkenyl, -OC(O)NR-substituted alkenyl, -OC(O)NR-alkynyl, -OC(O)NR-substituted alkynyl, -OC(O)NR-cycloalkyl, -OC(O)NR-substituted cycloalkyl, -OC(O)NR-aryl, -OC(O)NR-substituted aryl, -OC(O)NR-heteroaryl, -OC(O)NR-substituted heteroaryl,- OC(O)NR-heterocyclic, and -OC(O)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form, together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Oxythiocarbonylamino" refers to the groups -OC(S)NH_2,

-OC(S)NRR, -OC(S)NR-alkyl, -OC(S)NR-substituted alkyl, -OC(S)NR-alkenyl, -OC(S)NR-substituted alkenyl, -OC(S)NR-alkynyl, -OC(S)NR-substituted alkynyl, -OC(S)NR-cycloalkyl, -OC(S)NR-substituted cycloalkyl, -OC(S)NR-aryl, -OC(S)NR-substituted aryl, -OC(S)NR-heteroaryl, -OC(S)NR-substituted heteroaryl, -OC(S)NR-heterocyclic, and -OC(S)NR-substituted heterocyclic where R is hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminocarbonylamino" refers to the groups -NRC(O)NRR, -NRC(O)NR-alkyl, -NRC(O)NR-substituted alkyl, -NRC(O)NR-alkenyl, -NRC(O)NR-substituted alkenyl, -NRC(O)NR-alkynyl, -NRC(O)NR-substituted alkynyl, -NRC(O)NR-aryl, -NRC(O)NR-substituted aryl, -NRC(O)NR-cycloalkyl, -NRC(O)NR-substituted cycloalkyl, -NRC(O)NR-heteroaryl, and -NRC(O)NR-substituted heteroaryl, -NRC(O)NR-heterocyclic, and -NRC(O)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aminothiocarbonylamino" refers to the groups -NRC(S)NRR, -NRC(S)NR-alkyl, -NRC(S)NR-substituted alkyl, -NRC(S)NR-alkenyl,

-NRC(S)NR-substituted alkenyl, -NRC(S)NR-alkynyl, -NRC(S)NR-substituted alkynyl, -NRC(S)NR-aryl, -NRC(S)NR-substituted aryl, -NRC(S)NR-cycloalkyl, -NRC(S)NR-substituted cycloalkyl, -NRC(S)NR-heteroaryl, and -NRC(S)NR-substituted heteroaryl, -NRC(S)NR-heterocyclic, and -NRC(S)NR-substituted heterocyclic where each R is independently hydrogen, alkyl or where each R is joined to form together with the nitrogen atom a heterocyclic or substituted heterocyclic ring as well as where one of the amino groups is blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Aryl" or "Ar" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may or may not be aromatic (e.g., 2-benzoxazolinone, 2H-1,4-benzoxazin-3(4H)-one-7yl, and the like). Preferred aryls include phenyl and naphthyl.

Substituted aryl refers to aryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-

substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$S(O)_2$-alkyl, -$S(O)_2$-substituted alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-substituted cycloalkyl, -$S(O)_2$-alkenyl, -$S(O)_2$-substituted alkenyl, -$S(O)_2$-aryl, -$S(O)_2$-substituted aryl, -$S(O)_2$-heteroaryl, -$S(O)_2$-substituted heteroaryl, -$S(O)_2$-heterocyclic, -$S(O)_2$-substituted heterocyclic, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -OSO_2-NRR, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-substituted alkyl, -$NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, -$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,

heterocyclic, substituted heterocyclic, amino groups on the substituted aryl blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) or $-SO_2NRR$, where R is hydrogen or alkyl.

"Aryloxy" refers to the group aryl-O- which includes, by way of example, phenoxy, naphthoxy, and the like.

"Substituted aryloxy" refers to substituted aryl-O- groups.

"Aryloxyaryl" refers to the group -aryl-O-aryl.

"Substituted aryloxyaryl" refers to aryloxyaryl groups substituted with from 1 to 3 substituents on either or both aryl rings selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted

cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-cycloalkyl, $-S(O)_2$-substituted cycloalkyl, $-S(O)_2$-alkenyl, $-S(O)_2$-substituted alkenyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and amino groups on the substituted aryl blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) or $-SO_2NRR$, where R is hydrogen or alkyl.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl and the like. Excluded from this definition are multi-ring alkyl groups such as adamantanyl, etc.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 3 to 8 carbon atoms having single or multiple unsaturation but which are not aromatic.

"Substituted cycloalkyl" and "substituted cycloalkenyl" refer to a cycloalkyl and cycloalkenyl groups, preferably of from 3 to 8 carbon atoms, having from 1 to 5 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2-NRR$, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl,

-$NRS(O)_2$-NR-heteroaryl, -$NRS(O)_2$-NR-substituted heteroaryl, -$NRS(O)_2$-NR-heterocyclic, -$NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkynyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkynyl/substituted alkynyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl.

"Cycloalkoxy" refers to -O-cycloalkyl groups.

"Substituted cycloalkoxy" refers to -O-substituted cycloalkyl groups.

"Guanidino" refers to the groups -NRC(=NR)NRR, -NRC(=NR)NR-alkyl, -NRC(=NR)NR-substituted alkyl, -NRC(=NR)NR-alkenyl, -NRC(=NR)NR-substituted alkenyl, -NRC(=NR)NR-alkynyl, -NRC(=NR)NR-substituted alkynyl, -NRC(=NR)NR-aryl, -NRC(=NR)NR-substituted aryl, -NRC(=NR)NR-cycloalkyl, -NRC(=NR)NR-heteroaryl, -NRC(=NR)NR-substituted heteroaryl, -NRC(=NR)NR-heterocyclic, and -NRC(=NR)NR-substituted heterocyclic where each R is independently hydrogen and alkyl as well as

where one of the amino groups is blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Guanidinosulfone" refers to the groups -NRC(=NR)NRSO$_2$-alkyl, -NRC(=NR)NRSO$_2$-substituted alkyl, -NRC(=NR)NRSO$_2$-alkenyl, -NRC(=NR)NRSO$_2$-substituted alkenyl, -NRC(=NR)NRSO$_2$-alkynyl, -NRC(=NR)NRSO$_2$-substituted alkynyl, -NRC(=NR)NRSO$_2$-aryl, -NRC(=NR)NRSO$_2$-substituted aryl, -NRC(=NR)NRSO$_2$-cycloalkyl, -NRC(=NR)NRSO$_2$-substituted cycloalkyl, -NRC(=NR)NRSO$_2$-heteroaryl, -NRC(=NR)NRSO$_2$-substituted heteroaryl, -NRC(=NR)NRSO$_2$-heterocyclic, and -NRC(=NR)NRSO$_2$-substituted heterocyclic where each R is independently hydrogen and alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either chloro or bromo.

"Heteroaryl" refers to an aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl, indolyl and furyl.

"Substituted heteroaryl" refers to heteroaryl groups which are substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amidino, alkylamidino, thioamidino, amino, aminoacyl, aminocarbonyloxy, aminocarbonylamino, aminothiocarbonylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, carboxylamido, cyano, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thioheteroaryl, substituted thioheteroaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheterocyclic, substituted thioheterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, halo, nitro, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -$S(O)_2$-alkyl, -$S(O)_2$-substituted alkyl, -$S(O)_2$-cycloalkyl, -$S(O)_2$-substituted cycloalkyl, -$S(O)_2$-alkenyl, -$S(O)_2$-substituted alkenyl, -$S(O)_2$-aryl, -$S(O)_2$-substituted aryl, -$S(O)_2$-heteroaryl, -$S(O)_2$-substituted heteroaryl, -$S(O)_2$-heterocyclic, -$S(O)_2$-substituted heterocyclic, -$OS(O)_2$-alkyl, -$OS(O)_2$-substituted alkyl, -$OS(O)_2$-aryl, -$OS(O)_2$-substituted aryl, -$OS(O)_2$-heteroaryl, -$OS(O)_2$-substituted heteroaryl, -$OS(O)_2$-heterocyclic, -$OS(O)_2$-substituted heterocyclic, -OSO_2-NRR, -$NRS(O)_2$-alkyl, -$NRS(O)_2$-substituted alkyl, -$NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, -$NRS(O)_2$-heteroaryl, -$NRS(O)_2$-substituted heteroaryl, -$NRS(O)_2$-heterocyclic, -$NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, -$NRS(O)_2$-NR-

substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, amino groups on the substituted aryl blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like), and -SO$_2$NRR, where R is hydrogen or alkyl.

"Heteroaryloxy" refers to the group -O-heteroaryl and "substituted heteroaryloxy" refers to the group -O-substituted heteroaryl.

"Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 hetero atoms selected from the group consisting of nitrogen, sulfur or oxygen within the ring wherein, in fused ring systems, one or more the rings can be aryl or heteroaryl.

"Saturated heterocyclic" refers to heterocycles of single or multiple condensed rings lacking unsaturation in any ring (e.g., carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

"Unsaturated heterocyclic" refers to non-aromatic heterocycles of single or multiple condensed rings having unsaturation in any ring (e.g.,

carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

"Substituted heterocyclic" refers to heterocycle groups which are substituted with from 1 to 3 substituents selected from the group consisting of oxo (=O), thioxo (=S), alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, amino, amidino, alkylamidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, aryloxy, substituted aryloxy, aryloxyaryl, substituted aryloxyaryl, halogen, hydroxyl, cyano, nitro, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and

alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkynyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkynyl/substituted alkynyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl.

Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, thiomorpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

"Saturated substituted heterocyclic" refers to substituted heterocycles of single or multiple condensed rings lacking unsaturation in

any ring (e.g., carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

"Unsaturated substituted heterocyclic" refers to non-aromatic substituted heterocycles of single or multiple condensed rings having unsaturation in any ring (e.g., carbon to carbon unsaturation, carbon to nitrogen unsaturation, nitrogen to nitrogen unsaturation, and the like).

"Heterocyclyloxy" refers to the group -O-heterocyclic and "substituted heterocyclyloxy" refers to the group -O-substituted heterocyclic.

"Thiol" refers to the group -SH.

"Thioalkyl" refers to the groups -S-alkyl.

"Substituted thioalkyl" refers to the group -S-substituted alkyl.

"Thiocycloalkyl" refers to the groups -S-cycloalkyl.

"Substituted thiocycloalkyl" refers to the group -S-substituted cycloalkyl.

"Thioaryl" refers to the group -S-aryl and "substituted thioaryl" refers to the group -S-substituted aryl.

"Thioheteroaryl" refers to the group -S-heteroaryl and "substituted thioheteroaryl" refers to the group -S-substituted heteroaryl.

"Thioheterocyclic" refers to the group -S-heterocyclic and "substituted thioheterocyclic" refers to the group -S-substituted heterocyclic.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of Formula I or IA which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

Compound Preparation

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W.

Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

In a preferred method of synthesis, the compounds of formula I and IA wherein Q is $-C(O)NR^7-$ are prepared by first coupling an amino acid of formula II:

$$\begin{array}{c} R^3 \\ | \\ R^2\text{-NH-C-COOH} \\ | \\ H \end{array} \qquad \text{II}$$

wherein R^2 and R^3 are as defined above, with a sulfonyl chloride of formula III:

$$R^1\text{-}SO_2\text{-}Cl \qquad \text{III}$$

wherein R^1 is as defined above, to provide an *N*-sulfonyl amino acid of formula IV:

$$R^1\text{-}SO_2\text{-}N(R^2)\text{-}\overset{\displaystyle R^3 \atop |}{\underset{\displaystyle | \atop H}{C}}\text{-}COOH \qquad \text{IV}$$

wherein R^1-R^3 are as defined above.

This reaction is typically conducted by contacting the amino acid of formula II with at least one equivalent, preferably about 1.1 to about 2 equivalents, of sulfonyl chloride III in an inert diluent such as dichloromethane and the like. Generally, the reaction is conducted at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like, as the base. Upon completion of the reaction, the resulting *N*-sulfonyl amino acid IV is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

The amino acids of formula II employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Examples of suitable amino acids for use in this reaction include, but are not limited to, glycine,

2-*tert*-butylglycine, D,L-phenylglycine, L-alanine, α-methylalanine, *N*-methyl-L-phenylalanine, L-diphenylalanine, sarcosine, D,L-phenylsarcosine, L-aspartic acid β-*tert*-butyl ester, L-glutamic acid γ-*tert*-butyl ester, L-(*O*-benzyl)serine, 1-aminocyclopropanecarboxylic acid, 1-aminocyclobutanecarboxylic acid, 1-aminocyclopentanecarboxylic acid (cycloleucine) 1-aminocyclohexanecarboxylic acid, L-serine and the like. If desired, the corresponding carboxylic acid esters of the amino acids of formula II, such as the methyl esters, ethyl esters and the like, can be employed in the above reaction with the sulfonyl chloride III. Subsequent hydrolysis of the ester group to the carboxylic acid using conventional reagents and conditions, i.e., treatment with an alkali metal hydroxide in an inert diluent such as methanol/water, then provides the *N*-sulfonyl amino acid IV.

Similarly, the sulfonyl chlorides of formula III employed in the above reaction are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. Such compounds are typically prepared from the corresponding sulfonic acid, i.e., from compounds of the formula R^1-SO_3H where R^1 is as defined above, using phosphorous trichloride and phosphorous pentachloride. This reaction is generally conducted by contacting the sulfonic acid with about 2 to 5 molar equivalents of phosphorous trichloride and phosphorous pentachloride, either neat or in an inert solvent, such as dichloromethane, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours to afford the sulfonyl chloride. Alternatively, the sulfonyl chlorides of formula III can be prepared from the corresponding thiol compound, i.e., from compounds of the formula R^1-SH where R^1 is as defined above, by treating the thiol with chlorine (Cl_2) and water under conventional reaction conditions.

Examples of sulfonyl chlorides suitable for use in this invention include, but are not limited to, methanesulfonyl chloride, 2-propanesulfonyl chloride, 1-butanesulfonyl chloride, benzenesulfonyl chloride, 1-naphthalenesulfonyl chloride, 2-naphthalenesulfonyl chloride, *p*-toluenesulfonyl chloride, α-toluenesulfonyl chloride, 4-acetamidobenzenesulfonyl chloride, 4-amidinobenzenesulfonyl chloride, 4-*tert*-butylbenzenesulfonyl chloride, 4-bromobenzenesulfonyl chloride, 2-carboxybenzenesulfonyl chloride, 4-cyanobenzenesulfonyl chloride, 3,4-dichlorobenzenesulfonyl chloride, 3,5-dichlorobenzenesulfonyl chloride, 3,4-dimethoxybenzenesulfonyl chloride, 3,5-ditrifluoromethylbenzenesulfonyl chloride, 4-fluorobenzenesulfonyl chloride, 4-methoxybenzenesulfonyl chloride, 2-methoxycarbonylbenzenesulfonyl chloride, 4-methylamidobenzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, 4-thioamidobenzenesulfonyl chloride, 4-trifluoromethylbenzenesulfonyl chloride, 4-trifluoromethoxybenzenesulfonyl chloride, 2,4,6-trimethylbenzenesulfonyl chloride, 2-phenylethanesulfonyl chloride, 2-thiophenesulfonyl chloride, 5-chloro-2-thiophenesulfonyl chloride, 2,5-dichloro-4-thiophenesulfonyl chloride, 2-thiazolesulfonyl chloride, 2-methyl-4-thiazolesulfonyl chloride, 1-methyl-4-imidazolesulfonyl chloride, 1-methyl-4-pyrazolesulfonyl chloride, 5-chloro-1,3-dimethyl-4-pyrazolesulfonyl chloride, 3-pyridinesulfonyl chloride, 2-pyrimidinesulfonyl chloride, and the like. If desired, a sulfonyl fluoride, sulfonyl bromide or sulfonic acid anhydride may be used in place of the sulfonyl chloride in the above reaction to form the *N*-sulfonyl amino acids of formula IV.

The intermediate *N*-sulfonyl amino acids of formula IV, wherein R^3 is hydrogen, can also be prepared by reacting a sulfonamide of formula V:

$$R^1\text{-}SO_2\text{-}NH\text{-}R^2 \qquad \text{V}$$

wherein R^1 and R^2 are as defined above, with a carboxylic acid derivative of the formula $L(R^3)CHCOOR$ where L is a leaving group, such as chloro, bromo, iodo, mesylate, tosylate and the like, R^3 is as defined above and R is hydrogen or an alkyl group. This reaction is typically conducted by contacting the sulfonamide V with at least one equivalent, preferably 1.1 to 2 equivalents, of the carboxylic acid derivative in the presence of a suitable base, such as triethylamine, in an inert diluent, such as DMF, at a temperature ranging from about 24°C to about 37°C for about 0.5 to about 4 hours. This reaction is further described in Zuckermann et al., *J. Am. Chem. Soc.*, 1992, *114*, 10646-10647. Preferred carboxylic acid derivatives for use in this reaction are α-chloro and α-bromocarboxylic acid esters such as *tert*-butyl bromoacetate, and the like. When an carboxylic acid ester is employed in this reaction, the ester group is subsequently hydrolyzed using conventional procedures to afford an *N*-sulfonyl amino acid of formula IV.

The compounds of formula I are then prepared by coupling the intermediate *N*-sulfonyl amino acid of formula IV with an amino acid derivative of formula VI:

$$\begin{array}{c} \phantom{R^7\text{-NH-CH-}}\text{O} \\ \phantom{R^7\text{-NH-CH-}}\| \\ R^7\text{-NH-CH-C-}R^6 \\ \phantom{R^7\text{-NH-}}| \\ \phantom{R^7\text{-NH-}}R^5 \end{array} \qquad \text{VI}$$

wherein R^5-R^7 are as defined above. This coupling reaction is typically conducted using well-known coupling reagents such as carbodiimides, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphonate) and the like. Suitable carbodiimides include, by way of example, dicyclohexylcarbodiimide (DCC), 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and the like. If desired, polymer supported forms of carbodiimide coupling reagents may also be used including, for example, those described in *Tetrahedron Letters*, 34(48), 7685 (1993). Additionally, well-known coupling promoters, such as N-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be used to facilitate the coupling reaction.

This coupling reaction is typically conducted by contacting the *N*-sulfonylamino acid IV with about 1 to about 2 equivalents of the coupling reagent and at least one equivalent, preferably about 1 to about 1.2 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N,N*-dimethylformamide and the like. Generally, this reaction is conducted at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours. Upon completion of the reaction, the compound of formula I is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the *N*-sulfonyl amino acid IV can be converted into an acid halide and the acid halide coupled with amino acid derivative VI to provide compounds of formula I. The acid halide of VI can be prepared by contacting VI with an inorganic acid halide, such as thionyl chloride, phosphorous trichloride, phosphorous tribromide or phosphorous pentachloride, or preferably, with oxalyl chloride under conventional conditions. Generally, this reaction is conducted using about 1 to 5 molar equivalents of the inorganic acid halide or oxalyl chloride, either neat or in an inert solvent, such as dichloromethane or carbon tetrachloride, at temperature in the range of about 0°C to about 80°C for about 1 to about 48 hours. A catalyst, such as *N,N*-dimethylformamide, may also be used in this reaction.

The acid halide of *N*-sulfonyl amino acid IV is then contacted with at least one equivalent, preferably about 1.1 to about 1.5 equivalents, of amino acid derivative VI in an inert diluent, such as dichloromethane, at a temperature ranging from about -70°C to about 40°C for about 1 to about 24 hours. Preferably, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like. Upon completion of the reaction, the compound of formula I is recovered by conventional methods including neutralization, extraction, precipitation, chromatography, filtration, and the like.

Alternatively, the compounds of formula I can be prepared by first forming a diamino acid derivative of formula VII:

$$\begin{array}{ccccccccc} & & R^3 & & R^7 & & & O & \\ & & | & & | & & & \| & \\ R^2\text{-NH-} & & C & \text{-C(O)} & N & \text{-} & CH & \text{-}C\text{-} & R^6 \\ & & | & & & & | & & \\ & & H & & & & R^5 & & \end{array} \qquad \text{VII}$$

wherein R^2,R^3,R^{5-7} are as defined above. The diamino acid derivatives of formula VII can be readily prepared by coupling an amino acid of formula II with an amino acid derivative of formula VI using conventional amino acid coupling techniques and reagents, such carbodiimides, BOP reagent and the like, as described above. Diamino acid VII can then be sulfonated using a sulfonyl chloride of formula III and using the synthetic procedures described above to provide a compound of formula I.

The amino acid derivatives of formula VI employed in the above reactions are either known compounds or compounds that can be prepared from known compounds by conventional synthetic procedures. For example, amino acid derivatives of formula VI can be prepared by *C*-alkylating commercially available diethyl 2-acetamidomalonate (Aldrich, Milwaukee, Wisconsin, USA) with an alkyl or substituted alkyl halide. This reaction is typically conducted by treating the diethyl 2-acetamidomalonate with at least one equivalent of sodium ethoxide and at least one equivalent of an alkyl or substituted alkyl halide in refluxing ethanol for about 6 to about 12 hours. The resulting C-alkylated malonate is then deacetylated, hydrolyzed and decarboxylated by heating in aqueous hydrochloric acid at reflux for about 6 to about 12 hours to provide the amino acid, typically as the hydrochloride salt.

Examples of amino acid derivatives of formula VI suitable for use in the above reactions include, but are not limited to, L-alanine methyl ester, L-isoleucine methyl ester, L-leucine methyl ester, L-valine methyl ester, β-*tert*-butyl-L-aspartic acid methyl ester, L-asparagine *tert*-butyl ester, ε-Boc-L-lysine methyl ester, ε-Cbz-L-lysine methyl ester, γ-*tert*-butyl-L-glutamic acid methyl ester, L-glutamine *tert*-butyl ester, L-(*N*-methyl)histidine methyl ester, L-(*N*-benzyl)histidine methyl ester, L-methionine methyl ester, L-(*O*-benzyl)serine methyl ester, L-tryptophan methyl ester, L-phenylalanine methyl ester, L-phenylalanine isopropyl ester, L-phenylalanine benzyl ester, L-phenylalaninamide, *N*-methyl-L-phenylalanine benzyl ester, 3-carboxy-D,L-phenylalanine methyl ester, 4-carboxy-D,L-phenylalanine methyl ester, L-4-chlorophenylalanine methyl ester, L-4-(3-dimethylaminopropyloxy)phenylalanine methyl ester, L-4-iodophenylalanine methyl ester, L-3,4-methylenedioxyphenylalanine methyl ester, L-3,4-ethylenedioxyphenylalanine methyl ester, L-4-nitrophenylalanine methyl ester, L-tyrosine methyl ester, D,L-

homophenylalanine methyl ester, L-(*O*-methyl)tyrosine methyl ester, L-(*O*-*tert*-butyl)tyrosine methyl ester, L-(*O*-benzyl)tyrosine methyl ester, L-3,5-diiodotyrosine methyl ester, L-3-iodotyrosine methyl ester, β-(1-naphthyl)-L-alanine methyl ester, β-(2-naphthyl)-L-alanine methyl ester, β-(2-thienyl)-L-alanine methyl ester, β-cyclohexyl-L-alanine methyl ester, β-(2-pyridyl)-L-alanine methyl ester, β-(3-pyridyl)-L-alanine methyl ester, β-(4-pyridyl)-L-alanine methyl ester, β-(2-thiazolyl)-D,L-alanine methyl ester, β-(1,2,4-triazol-3-yl)-D,L-alanine methyl ester, and the like. If desired, of course, other esters or amides of the above-described compounds may also be employed.

For ease of synthesis, the compounds of formula I are typically prepared as an ester, i.e., where R^6 is an alkoxy or substituted alkoxy group and the like. If desired, the ester group can be hydrolysed using conventional conditions and reagents to provide the corresponding carboxylic acid. Typically, this reaction is conducted by treating the ester with at least one equivalent of an alkali metal hydroxide, such as lithium, sodium or potassium hydroxide, in an inert diluent, such as methanol or mixtures of methanol and water, at a temperature ranging about 0°C to about 24°C for about 1 to about 12 hours. Alternatively, benzyl esters may be removed by hydrogenolysis using a palladium catalyst, such as palladium on carbon. The resulting carboxylic acids may be coupled, if desired, to amines such as β-alanine ethyl ester, hydroxyamines such as hydroxylamine and *N*-hydroxysuccinimide, alkoxyamines and substituted alkoxyamines such as *O*-methylhydroxylamine and *O*-benzylhydroxylamine, and the like, using conventional coupling reagents and conditions as described above.

As will be apparent to those skilled in the art, other functional groups present on any of the substituents of the compounds of formula I

can be readily modified or derivatized either before or after the above-described coupling reactions using well-known synthetic procedures. For example, a nitro group present on a substituent of a compound of formula I or an intermediate thereof may be readily reduced by hydrogenation in the presence of a palladium catalyst, such as palladium on carbon, to provide the corresponding amino group. This reaction is typically conducted at a temperature of from about 20°C to about 50°C for about 6 to about 24 hours in an inert diluent, such as methanol. Compounds having a nitro group on the R^5 substituent can be prepared, for example, by using a 4-nitrophenylalanine derivative and the like in the above-described coupling reactions.

Similarly, a pyridyl group can be hydrogenated in the presence of a platinum catalyst, such as platinum oxide, in an acidic diluent to provide the corresponding piperidinyl analogue. Generally, this reaction is conducted by treating the pyridine compound with hydrogen at a pressure ranging from about 20 psi to about 60 psi, preferably about 40 psi, in the presence of the catalyst at a temperature of about 20°C to about 50°C for about 2 to about 24 hours in an acidic diluent, such as a mixture of methanol and aqueous hydrochloric acid. Compounds having a pyridyl group can be readily prepared by using, for example, β-(2-pyridyl)-, β-(3-pyridyl)- or β-(4-pyridyl)-L-alanine derivatives in the above-described coupling reactions.

Additionally, when the R^5 substituent of a compound of formula I or an intermediate thereof contains a primary or secondary amino group, such amino groups can be further derivatized either before or after the above coupling reactions to provide, by way of example, amides, sulfonamides, ureas, thioureas, carbamates, secondary or tertiary amines and the like. Compounds having a primary amino group on the R^5 substituent may be

prepared, for example, by reduction of the corresponding nitro compound as described above. Alternatively, such compounds can be prepared by using an amino acid derivative of formula VI derived from lysine, 4-aminophenylalanine and the like in the above-described coupling reactions.

By way of illustration, a compound of formula I or an intermediate thereof having a substituent containing a primary or secondary amino group, such as where R^5 is a (4-aminophenyl)methyl group, can be readily *N*-acylated using conventional acylating reagents and conditions to provide the corresponding amide. This acylation reaction is typically conducted by treating the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of a carboxylic acid in the presence of a coupling reagent such as a carbodiimide, BOP reagent (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphonate) and the like, in an inert diluent, such as dichloromethane, chloroform, acetonitrile, tetrahydrofuran, *N*,*N*-dimethylformamide and the like, at a temperature ranging from about 0°C to about 37°C for about 4 to about 24 hours. Preferably, a promoter, such as *N*-hydroxysuccinimide, 1-hydroxy-benzotriazole and the like, is used to facilitate the acylation reaction. Examples of carboxylic acids suitable for use in this reaction include, but are not limited to, *N*-*tert*-butyloxycarbonylglycine, *N*-*tert*-butyloxycarbonyl-L-phenylalanine, *N*-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester, benzoic acid, *N*-*tert*-butyloxycarbonylisonipecotic acid, *N*-methylisonipecotic acid, *N*-*tert*-butyloxycarbonylnipecotic acid, *N*-*tert*-butyloxycarbonyl-L-tetrahydroisoquinoline-3-carboxylic acid, *N*-(toluene-4-sulfonyl)-L-proline and the like.

Alternatively, a compound of formula I or an intermediate thereof containing a primary or secondary amino group can be *N*-acylated using an acyl halide or a carboxylic acid anhydride to form the corresponding

amide. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the acyl halide or carboxylic acid anhydride in an inert diluent, such as dichloromethane, at a temperature ranging from about of about -70°C to about 40°C for about 1 to about 24 hours. If desired, an acylation catalyst such as 4-(*N*,*N*-dimethylamino)pyridine may be used to promote the acylation reaction. The acylation reaction is preferably conducted in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Alternatively, the reaction can be conducted under Schotten-Baumann-type conditions using aqueous alkali, such as sodium hydroxide and the like.

Examples of acyl halides and carboxylic acid anhydrides suitable for use in this reaction include, but are not limited to, 2-methylpropionyl chloride, trimethylacetyl chloride, phenylacetyl chloride, benzoyl chloride, 2-bromobenzoyl chloride, 2-methylbenzoyl chloride, 2-trifluoro-methylbenzoyl chloride, isonicotinoyl chloride, nicotinoyl chloride, picolinoyl chloride, acetic anhydride, succinic anhydride, and the like. Carbamyl chlorides, such as *N*,*N*-dimethylcarbamyl chloride, *N*,*N*-diethylcarbamyl chloride and the like, can also be used in this reaction to provide ureas. Similarly, dicarbonates, such as di-*tert*-butyl dicarbonate, may be employed to provide carbamates.

In a similar manner, a compound of formula I or an intermediate thereof containing a primary or secondary amino group may be *N*-sulfonated to form a sulfonamide using a sulfonyl halide or a sulfonic acid anhydride. Sulfonyl halides and sulfonic acid anhydrides suitable for use in this reaction include, but are not limited to, methanesulfonyl chloride,

chloromethanesulfonyl chloride, *p*-toluenesulfonyl chloride, trifluoromethanesulfonic anhydride, and the like. Similarly, sulfamoyl chlorides, such as dimethylsulfamoyl chloride, can be used to provide sulfamides (e.g., $>N-SO_2-N<$).

Additionally, a primary and secondary amino group present on a substituent of a compound of formula I or an intermediate thereof can be reacted with an isocyanate or a thioisocyanate to give a urea or thiourea, respectively. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to about 1.2 equivalents, of the isocyanate or thioisocyanate in an inert diluent, such as toluene and the like, at a temperature ranging from about 24°C to about 37°C for about 12 to about 24 hours. The isocyanates and thioisocyanates used in this reaction are commercially available or can be prepared from commercially available compounds using well-known synthetic procedures. For example, isocyanates and thioisocyanates are readily prepared by reacting the appropriate amine with phosgene or thiophosgene. Examples of isocyanates and thioisocyanates suitable for use in this reaction include, but are not limited to, ethyl isocyanate, *n*-propyl isocyanate, 4-cyanophenyl isocyanate, 3-methoxyphenyl isocyanate, 2-phenylethyl isocyanate, methyl thioisocyanate, ethyl thioisocyanate, 2-phenylethyl thioisocyanate, 3-phenylpropyl thioisocyanate, 3-(*N*,*N*-diethylamino)propyl thioisocyanate, phenyl thioisocyanate, benzyl thioisocyanate, 3-pyridyl thioisocyanate, fluorescein isothiocyanate (isomer I) and the like.

Furthermore, when a compound of formula I or an intermediate thereof contains a primary or secondary amino group, the amino group can be reductively alkylated using aldehydes or ketones to form a secondary or tertiary amino group. This reaction is typically conducted by contacting the amino compound with at least one equivalent, preferably about 1.1 to

about 1.5 equivalents, of an aldehyde or ketone and at least one equivalent based on the amino compound of a metal hydride reducing agent, such as sodium cyanoborohydride, in an inert diluent, such as methanol, tetrahydrofuran, mixtures thereof and the like, at a temperature ranging from about 0°C to about 50°C for about 1 to about 72 hours. Aldehydes and ketones suitable for use in this reaction include, by way of example, benzaldehyde, 4-chlorobenzaldehyde, valeraldehyde and the like.

In a similar manner, when a compound of formula I or an intermediate thereof has a substituent containing a hydroxyl group, the hydroxyl group can be further modified or derivatized either before or after the above coupling reactions to provide, by way of example, ethers, carbamates and the like. Compounds having a hydroxyl group on the R^5 substituent, for example, can be prepared using an amino acid derivative of formula VI derived from tyrosine and the like in the above-described reactions.

By way of example, a compound of formula I or an intermediate thereof having a substituent containing a hydroxyl group, such as where R^5 is a (4-hydroxyphenyl)methyl group, can be readily *O*-alkylated to form ethers. This *O*-alkylation reaction is typically conducted by contacting the hydroxy compound with a suitable alkali or alkaline earth metal base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and the like, to form the alkali or alkaline earth metal salt of the hydroxyl group. This salt is generally not isolated, but is reacted *in situ* with at least one equivalent of an alkyl or substituted alkyl halide or sulfonate, such as an alkyl chloride, bromide, iodide, mesylate or tosylate, to afford the ether. Generally, this reaction is conducted at a temperature ranging from about 60°C to about 150°C for about 24 to about 72 hours. Preferably, a

catalytic amount of sodium or potassium iodide is added to the reaction mixture when an alkyl chloride or bromide is employed in the reaction.

Examples of alkyl or substituted alkyl halides and sulfonates suitable for use in this reaction include, but are not limited to, *tert*-butyl bromoacetate, *N-tert*-butyl chloroacetamide, 1-bromoethylbenzene, ethyl α-bromophenylacetate, 2-(*N*-ethyl-*N*-phenylamino)ethyl chloride, 2-(*N*,*N*-ethylamino)ethyl chloride, 2-(*N*,*N*-diisopropylamino)ethyl chloride, 2-(*N*,*N*-dibenzylamino)ethyl chloride, 3-(*N*,*N*-ethylamino)propyl chloride, 3-(*N*-benzyl-*N*-methylamino)propyl chloride, *N*-(2-chloroethyl)morpholine, 2-(hexamethyleneimino)ethyl chloride, 3-(*N*-methylpiperazine)propyl chloride, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine, 2-(4-hydroxy-4-phenylpiperidine)ethyl chloride, *N-tert*-butyloxycarbonyl-3-piperidinemethyl tosylate, and the like.

Alternatively, a hydroxyl group present on a substituent of a compound of formula I or an intermediate thereof can be *O*-alkylating using the Mitsunobu reaction. In this reaction, an alcohol, such as 3-(*N*,*N*-dimethylamino)-1-propanol and the like, is reacted with about 1.0 to about 1.3 equivalents of triphenylphosphine and about 1.0 to about 1.3 equivalents of diethyl azodicarboxylate in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about -10°C to about 5°C for about 0.25 to about 1 hour. About 1.0 to about 1.3 equivalents of a hydroxy compound, such as *N-tert*-butyltyrosine methyl ester, is then added and the reaction mixture is stirred at a temperature of about 0°C to about 30°C for about 2 to about 48 hours to provide the *O*-alkylated product.

In a similar manner, a compound of formula I or an intermediate thereof containing a aryl hydroxy group can be reacted with an aryl iodide to provide a diaryl ether. Generally, this reaction is conducted by forming

the alkali metal salt of the hydroxyl group using a suitable base, such as sodium hydride, in an inert diluent such as xylenes at a temperature of about -25°C to about 10°C. The salt is then treated with about 1.1 to about 1.5 equivalents of cuprous bromide dimethyl sulfide complex at a temperature ranging from about 10°C to about 30°C for about 0.5 to about 2.0 hours, followed by about 1.1 to about 1.5 equivalents of an aryl iodide, such as sodium 2-iodobenzoate and the like. The reaction is then heated to about 70°C to about 150°C for about 2 to about 24 hours to provide the diaryl ether.

Additionally, a hydroxy-containing compound can also be readily derivatized to form a carbamate. In one method for preparing such carbamates, a hydroxy compound of formula I or an intermediate thereof is contacted with about 1.0 to about 1.2 equivalents of 4-nitrophenyl chloroformate in an inert diluent, such as dichloromethane, at a temperature ranging from about -25°C to about 0°C for about 0.5 to about 2.0 hours. Treatment of the resulting carbonate with an excess, preferably about 2 to about 5 equivalents, of a trialkylamine, such as triethylamine, for about 0.5 to 2 hours, followed by about 1.0 to about 1.5 equivalents of a primary or secondary amine provides the carbamate. Examples of amines suitable for using in this reaction include, but are not limited to, piperazine, 1-methylpiperazine, 1-acetylpiperazine, morpholine, thiomorpholine, pyrrolidine, piperidine and the like.

Alternatively, in another method for preparing carbamates, a hydroxy-containing compound is contacted with about 1.0 to about 1.5 equivalents of a carbamyl chloride in an inert diluent, such as dichloromethane, at a temperature ranging from about 25°C to about 70°C for about 2 to about 72 hours. Typically, this reaction is conducted in the presence of a suitable base to scavenge the acid generated during the

reaction. Suitable bases include, by way of example, tertiary amines, such as triethylamine, diisopropylethylamine, *N*-methylmorpholine and the like. Additionally, at least one equivalent (based on the hydroxy compound) of 4-(*N*,*N*-dimethylamino)pyridine is preferably added to the reaction mixture to facilitate the reaction. Examples of carbamyl chlorides suitable for use in this reaction include, by way of example, dimethylcarbamyl chloride, diethylcarbamyl chloride and the like.

Likewise, when a compound of formula I or an intermediate thereof contains a primary or secondary hydroxyl group, such hydroxyl groups can be readily converted into a leaving group and displaced to form, for example, amines, sulfides and fluorides. For example, derivatives of 4-hydroxy-L-proline can be converted into the corresponding 4-amino, 4-thio or 4-fluoro-L-proline derivatives via nucleophilic displacement of the derivatized hydroxyl group. Generally, when a chiral compound is employed in these reactions, the stereochemistry at the carbon atom attached to the derivatized hydroxyl group is typically inverted.

These reactions are typically conducted by first converting the hydroxyl group into a leaving group, such as a tosylate, by treatment of the hydroxy compound with at least one equivalent of a sulfonyl halide, such as *p*-toluenesulfonyl chloride and the like, in pyridine. This reaction is generally conducted at a temperature of from about 0°C to about 70°C for about 1 to about 48 hours. The resulting tosylate can then be readily displaced with sodium azide, for example, by contacting the tosylate with at least one equivalent of sodium azide in an inert diluent, such as a mixture of *N*,*N*-dimethylformamide and water, at a temperature ranging from about 0°C to about 37°C for about 1 to about 12 hours to provide the corresponding azido compound. The azido group can then be reduced by,

for example, hydrogenation using a palladium on carbon catalyst to provide the amino ($-NH_2$) compound.

Similarly, a tosylate group can be readily displaced by a thiol to form a sulfide. This reaction is typically conducted by contacting the tosylate with at least one equivalent of a thiol, such as thiophenol, in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in an inert diluent, such as *N*,*N*-dimethylformamide, at a temperature of from about 0°C to about 37°C for about 1 to about 12 hours to provide the sulfide. Additionally, treatment of a tosylate with morpholinosulfur trifluoride in an inert diluent, such as dichloromethane, at a temperature ranging from about 0°C to about 37°C for about 12 to about 24 hours affords the corresponding fluoro compound.

Furthermore, a compound of formula I or an intermediate thereof having a substituent containing an iodoaryl group, for example, when R^5 is a (4-iodophenyl)methyl group, can be readily converted either before or after the above coupling reactions into a biaryl compound. Typically, this reaction is conducted by treating the iodoaryl compound with about 1.1 to about 2 equivalents of an arylzinc iodide, such as 2-(methoxycarbonyl)phenylzinc iodide, in the presence of a palladium catalyst, such as palladium tetra(triphenylphosphine), in an inert diluent, such as tetrahydrofuran, at a temperature ranging from about 24°C to about 30°C until reaction completion. This reaction is further described, for example, in Rieke, *J. Org. Chem.* **1991**, *56*, 1445.

In some cases, the compounds of formula I or IA or intermediates thereof may contain substituents having one or more sulfur atoms. Such sulfur atoms will be present, for example, when the amino acid of formula II employed in the above reactions is derived from L-thiazolidine-4-

carboxylic acid, L-(5,5-dimethyl)thiazolidine-4-carboxylic acid, L-thiamorpholine-3-carboxylic acid and the like. When present, such sulfur atoms can be oxidized either before or after the above coupling reactions to provide a sulfoxide or sulfone compound using conventional reagents and reaction conditions. Suitable reagents for oxidizing a sulfide compound to a sulfoxide include, by way of example, hydrogen peroxide, 3-chloroperoxybenzoic acid (MCPBA), sodium periodate and the like. The oxidation reaction is typically conducted by contacting the sulfide compound with about 0.95 to about 1.1 equivalents of the oxidizing reagent in an inert diluent, such as dichloromethane, at a temperature ranging from about -50°C to about 75°C for about 1 to about 24 hours. The resulting sulfoxide can then be further oxidized to the corresponding sulfone by contacting the sulfoxide with at least one additional equivalent of an oxidizing reagent, such as hydrogen peroxide, MCPBA, potassium permanganate and the like. Alternatively, the sulfone can be prepared directly by contacting the sulfide with at least two equivalents, and preferably an excess, of the oxidizing reagent. Such reactions are described further in March, "*Advanced Organic Chemistry*", 4th Ed., pp. 1201-1202, Wiley Publisher, 1992.

As described above, the compounds of formula I having an R^2 substituent other an hydrogen can be prepared using an *N*-substituted amino acid of formula II, such as sarcosine, *N*-methyl-L-phenylalanine and the like, in the above-described coupling reactions. Alternatively, such compounds can be prepared by *N*-alkylation of a sulfonamide of formula I or IV (where R^2 is hydrogen) using conventional synthetic procedures. Typically, this *N*-alkylation reaction is conducted by contacting the sulfonamide with at least one equivalent, preferably 1.1 to 2 equivalents, of an alkyl or substituted alkyl halide in the presence of a suitable base, such as potassium carbonate, in an inert diluent, such as acetone, 2-butanone and

the like, at a temperature ranging from about 25°C to about 70°C for about 2 to about 48 hours. Examples of alkyl or substituted alkyl halides suitable for use in this reaction include, but are not limited to, methyl iodide, and the like.

Additionally, the sulfonamides of formula I or IV wherein R^2 is hydrogen and R^1 is a 2-alkoxycarbonylaryl group can be intramolecularly cyclized to form 1,2-benzisothiazol-3-one derivatives or analogues thereof. This reaction is typically conducted by treating a sulfonamide, such as *N*-(2-methoxycarbonylphenylsulfonyl)glycine-L-phenylalanine benzyl ester, with about 1.0 to 1.5 equivalents of a suitable base, such as an alkali metal hydride, in a inert diluent, such as tetrahydrofuran, at a temperature ranging from about 0°C to about 30°C for about 2 to about 48 hours to afford the cyclized 1,2-benzisothiazol-3-one derivative.

Lastly, the compounds of formula I where Q is -C(S)NR^7- are can prepared by using an amino thionoacid derivative in place of amino acid II in the above described synthetic procedures. Such amino thionoacid derivatives can be prepared by the procedures described in Shalaky, et al., *J. Org. Chem.*, 61:9045-9048 (1996) and Brain, et al., *J. Org. Chem.*, 62:3808-3809 (1997) and references cited therein.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of formula I and IA are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a

manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I and IA above associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The

formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active

ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*.

Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The following formulation examples illustrate the pharmaceutical compositions of the present invention.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium

carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the

minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%) Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Direct techniques can be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Utility

The compounds of this invention can be employed to bind VLA-4 ($\alpha_4\beta_1$ integrin) in biological samples and, accordingly have utility in, for example, assaying such samples for VLA-4. In such assays, the compounds can be bound to a solid support and the VLA-4 sample added thereto. The amount of VLA-4 in the sample can be determined by conventional methods such as use of a sandwich ELISA assay. Alternatively, labeled VLA-4 can be used in a competitive binding assay to measure for the presence of VLA-4 in the sample. Other suitable assays are well known in the art.

In addition, certain of the compounds of this invention inhibit, *in vivo*, adhesion of leukocytes to endothelial cells mediated by VLA-4 and, accordingly, can be used in the treatment of diseases mediated by VLA-4. Such diseases include inflammatory diseases in mammalian patients such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

The biological activity of the compounds identified above may be assayed in a variety of systems. For example, a compound can be immobilized on a solid surface and adhesion of cells expressing VLA-4 can be measured. Using such formats, large numbers of compounds can be screened. Cells suitable for this assay include any leukocytes known to express VLA-4 such as T cells, B cells, monocytes, eosinophils, and

basophils. A number of leukocyte cell lines can also be used, examples include Jurkat and U937.

The test compounds can also be tested for the ability to competitively inhibit binding between VLA-4 and VCAM-1, or between VLA-4 and a labeled compound known to bind VLA-4 such as a compound of this invention or antibodies to VLA-4. In these assays, the VCAM-1 can be immobilized on a solid surface. VCAM-1 may also be expressed as a recombinant fusion protein having an Ig tail (e.g., IgG) so that binding to VLA-4 may be detected in an immunoassay. Alternatively, VCAM-1 expressing cells, such as activated endothelial cells or VCAM-1 transfected fibroblasts can be used. For assays to measure the ability to block adhesion to brain endothelial cells, the assays described in International Patent Application Publication No. WO 91/05038 are particularly preferred. This application is incorporated herein by reference in its entirety.

Many assay formats employ labelled assay components. The labelling systems can be in a variety of forms. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labelled by any one of several methods. The most common method of detection is the use of autoradiography with ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P labelled compounds and the like. Non-radioactive labels include ligands which bind to labelled antibodies, fluorophores, chemiluminescent agents, enzymes and antibodies which can serve as specific binding pair members for a labelled ligand. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation.

Appropriate *in vivo* models for demonstrating efficacy in treating inflammatory responses include EAE (experimental autoimmune encephalomyelitis) in mice, rats, guinea pigs or primates, as well as other inflammatory models dependent upon α4 integrins.

Compounds having the desired biological activity may be modified as necessary to provide desired properties such as improved pharmacological properties (e.g., *in vivo* stability, bio-availability), or the ability to be detected in diagnostic applications. For instance, inclusion of one or more D-amino acids in the sulfonamides of this invention typically increases *in vivo* stability. Stability can be assayed in a variety of ways such as by measuring the half-life of the proteins during incubation with peptidases or human plasma or serum. A number of such protein stability assays have been described (see, e.g., Verhoef et al., Eur. J. Drug Metab. Pharmacokinet., 1990, 15(2):83-93).

For diagnostic purposes, a wide variety of labels may be linked to the compounds, which may provide, directly or indirectly, a detectable signal. Thus, the compounds of the subject invention may be modified in a variety of ways for a variety of end purposes while still retaining biological activity. In addition, various reactive sites may be introduced at the terminus for linking to particles, solid substrates, macromolecules, and the like.

Labeled compounds can be used in a variety of *in vivo* or *in vitro* applications. A wide variety of labels may be employed, such as radionuclides (e.g., gamma-emitting radioisotopes such as technetium-99 or indium-111), fluorescers (e.g., fluorescein), enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chemiluminescent compounds, bioluminescent compounds, and the like. Those of ordinary skill in the art

will know of other suitable labels for binding to the complexes, or will be able to ascertain such using routine experimentation. The binding of these labels is achieved using standard techniques common to those of ordinary skill in the art.

In vitro uses include diagnostic applications such as monitoring inflammatory responses by detecting the presence of leukocytes expressing VLA-4. The compounds of this invention can also be used for isolating or labeling such cells. In addition, as mentioned above, the compounds of the invention can be used to assay for potential inhibitors of VLA-4/VCAM-1 interactions.

For *in vivo* diagnostic imaging to identify, e.g., sites of inflammation, radioisotopes are typically used in accordance with well known techniques. The radioisotopes may be bound to the peptide either directly or indirectly using intermediate functional groups. For instance, chelating agents such as diethylenetriaminepentacetic acid (DTPA) and ethylenediaminetetraacetic acid (EDTA) and similar molecules have been used to bind proteins to metallic ion radioisotopes.

The complexes can also be labeled with a paramagnetic isotope for purposes of *in vivo* diagnosis, as in magnetic resonance imaging (MRI) or electron spin resonance (ESR), both of which are well known. In general, any conventional method for visualizing diagnostic images can be used. Usually gamma- and positron-emitting radioisotopes are used for camera imaging and paramagnetic isotopes are used for MRI. Thus, the compounds can be used to monitor the course of amelioration of an inflammatory response in an individual. By measuring the increase or decrease in lymphocytes expressing VLA-4 it is possible to determine

whether a particular therapeutic regimen aimed at ameliorating the disease is effective.

The pharmaceutical compositions of the present invention can be used to block or inhibit cellular adhesion associated with a number of diseases and disorders. For instance, a number of inflammatory disorders are associated with integrins or leukocytes. Treatable disorders include, e.g., transplantation rejection (e.g., allograft rejection), Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), retinitis, cancer metastases, rheumatoid arthritis, acute leukocyte-mediated lung injury (e.g., adult respiratory distress syndrome), asthma, nephritis, and acute and chronic inflammation, including atopic dermatitis, psoriasis, myocardial ischemia, and inflammatory bowel disease (including Crohn's disease and ulcerative colitis). In preferred embodiments the pharmaceutical compositions are used to treat inflammatory brain disorders, such as multiple sclerosis (MS), viral meningitis and encephalitis.

Inflammatory bowel disease is a collective term for two similar diseases referred to as Crohn's disease and ulcerative colitis. Crohn's disease is an idiopathic, chronic ulceroconstrictive inflammatory disease characterized by sharply delimited and typically transmural involvement of all layers of the bowel wall by a granulomatous inflammatory reaction. Any segment of the gastrointestinal tract, from the mouth to the anus, may be involved, although the disease most commonly affects the terminal ileum and/or colon. Ulcerative colitis is an inflammatory response limited largely to the colonic mucosa and submucosa. Lymphocytes and macrophages are numerous in lesions of inflammatory bowel disease and may contribute to inflammatory injury.

Asthma is a disease characterized by increased responsiveness of the tracheobronchial tree to various stimuli potentiating paroxysmal constriction of the bronchial airways. The stimuli cause release of various mediators of inflammation from IgE-coated mast cells including histamine, eosinophilic and neutrophilic chemotactic factors, leukotrines, prostaglandin and platelet activating factor. Release of these factors recruits basophils, eosinophils and neutrophils, which cause inflammatory injury.

Atherosclerosis is a disease of arteries (e.g., coronary, carotid, aorta and iliac). The basic lesion, the atheroma, consists of a raised focal plaque within the intima, having a core of lipid and a covering fibrous cap. Atheromas compromise arterial blood flow and weaken affected arteries. Myocardial and cerebral infarcts are a major consequence of this disease. Macrophages and leukocytes are recruited to atheromas and contribute to inflammatory injury.

Rheumatoid arthritis is a chronic, relapsing inflammatory disease that primarily causes impairment and destruction of joints. Rheumatoid arthritis usually first affects the small joints of the hands and feet but then may involve the wrists, elbows, ankles and knees. The arthritis results from interaction of synovial cells with leukocytes that infiltrate from the circulation into the synovial lining of the joints. See *e.g.*, Paul, *Immunology* (3d ed., Raven Press, 1993).

Another indication for the compounds of this invention is in treatment of organ or graft rejection mediated by VLA-4. Over recent years there has been a considerable improvement in the efficiency of surgical techniques for transplanting tissues and organs such as skin, kidney, liver, heart, lung, pancreas and bone marrow. Perhaps the principal outstanding

problem is the lack of satisfactory agents for inducing immunotolerance in the recipient to the transplanted allograft or organ. When allogenetic cells or organs are transplanted into a host (i.e., the donor and donee are different individuals from the same species), the host immune system is likely to mount an immune response to foreign antigens in the transplant (host-versus-graft disease) leading to destruction of the transplanted tissue. $CD8^+$ cells, CD4 cells and monocytes are all involved in the rejection of transplant tissues. Compounds of this invention which bind to alpha-4 integrin are useful, *inter alia*, to block alloantigen-induced immune responses in the donee thereby preventing such cells from participating in the destruction of the transplanted tissue or organ. See, *e.g.*, Paul et al., *Transplant International* 9, 420-425 (1996); Georczynski et al., *Immunology* 87, 573-580 (1996); Georcyznski et al., *Transplant. Immunol.* 3, 55-61 (1995); Yang et al., *Transplantation* 60, 71-76 (1995); Anderson et al., *APMIS* 102, 23-27 (1994).

A related use for compounds of this invention which bind to VLA-4 is in modulating the immune response involved in "graft versus host" disease (GVHD). See *e.g.*, Schlegel et al., *J. Immunol.* 155, 3856-3865 (1995). GVHD is a potentially fatal disease that occurs when immunologically competent cells are transferred to an allogenetic recipient. In this situation, the donor's immunocompetent cells may attack tissues in the recipient. Tissues of the skin, gut epithelia and liver are frequent targets and may be destroyed during the course of GVHD. The disease presents an especially severe problem when immune tissue is being transplanted, such as in bone marrow transplantation; but less severe GVHD has also been reported in other cases as well, including heart and liver transplants. The therapeutic agents of the present invention are used, *inter alia*, to block activation of the donor T-cells thereby interfering with their ability to lyse target cells in the host.

A further use of the compounds of this invention is inhibiting tumor metastasis. Several tumor cells have been reported to express VLA-4 and compounds which bind VLA-4 block adhesion of such cells to endothelial cells. Steinback et al., *Urol. Res.* 23, 175-83 (1995); Orosz et al., *Int. J. Cancer* 60, 867-71 (1995); Freedman et al., *Leuk. Lymphoma* 13, 47-52 (1994); Okahara et al., *Cancer Res.* 54, 3233-6 (1994).

A further use of the compounds of this invention is in treating multiple sclerosis. Multiple sclerosis is a progressive neurological autoimmune disease that affects an estimated 250,000 to 350,000 people in the United States. Multiple sclerosis is thought to be the result of a specific autoimmune reaction in which certain leukocytes attack and initiate the destruction of myelin, the insulating sheath covering nerve fibers. In an animal model for multiple sclerosis, murine monoclonal antibodies directed against VLA-4 have been shown to block the adhesion of leukocytes to the endothelium, and thus prevent inflammation of the central nervous system and subsequent paralysis in the animals[16].

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences,* Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

In order to enhance serum half-life, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference.

The amount administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the compounds of the present invention will vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for intravenous administration, the dose will typically be in the range of about 20 μg to about 500 μg per kilogram body weight, preferably

about 100 μg to about 300 μg per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.1 pg to 1 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention. Unless otherwise stated, all temperatures are in degrees Celsius.

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

aq or aq.	=	aqueous
AcOH	=	acetic acid
bd	=	broad doublet
bm	=	broad multiplet
bs	=	broad singlet
Bn	=	benzyl
Boc	=	*N-tert*-butoxylcarbonyl
Boc_2O	=	di-*tert*-butyl dicarbonate
BOP	=	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
Cbz	=	carbobenzyloxy
$CHCl_3$	=	chloroform
CH_2Cl_2	=	dichloromethane
$(COCl)_2$	=	oxalyl chloride
d	=	doublet
dd	=	doublet of doublets
dt	=	doublet of triplets
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	=	1,3-dicyclohexylcarbodiimide
DMAP	=	4-*N,N*-dimethylaminopyridine
DME	=	ethylene glycol dimethyl ether
DMF	=	*N,N*-dimethylformamide

DMSO	=	dimethylsulfoxide
EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	=	triethylamine
Et_2O	=	diethyl ether
EtOAc	=	ethyl acetate
EtOH	=	ethanol
eq or eq.	=	equivalent
Fmoc	=	*N*-(9-fluorenylmethoxycarbonyl)
FmocONSu	=	*N*-(9-fluorenylmethoxycarbonyl)-succinimide
g	=	grams
h	=	hour
H_2O	=	water
HBr	=	hydrobromic acid
HCl	=	hydrochloric acid
HOBT	=	1-hydroxybenzotriazole hydrate
hr	=	hour
K_2CO_3	=	potassium carbonate
L	=	liter
m	=	multiplet
MeOH	=	methanol
mg	=	milligram
$MgSO_4$	=	magnesium sulfate
mL	=	milliliter
mm	=	millimeter
mM	=	millimolar
mmol	=	millimol
mp	=	melting point
N	=	normal
NaCl	=	sodium chloride
Na_2CO_3	=	sodium carbonate
$NaHCO_3$	=	sodium bicarbonate
NaOEt	=	sodium ethoxide
NaOH	=	sodium hydroxide
NH_4Cl	=	ammonium chloride
NMM	=	*N*-methylmorpholine
Phe	=	L-phenylalanine
Pro	=	L-proline
psi	=	pounds per square inch
PtO_2	=	platinum oxide
q	=	quartet
quint.	=	quintet
rt	=	room temperature

s	=	singlet
sat	=	saturated
t	=	triplet
t-BuOH	=	*tert*-butanol
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC or tlc	=	thin layer chromatography
Ts	=	tosyl
TsCl	=	tosyl chloride
TsOH	=	tosylate
μL	=	microliter

In the examples below, all temperatures are in degrees Celcius (unless otherwise indicated). The following Methods were used to prepare the compounds set forth below as indicated.

Method 1

N-Tosylation Procedure

N-Tosylation of the appropriate amino acid was conducted via the method of Cupps, Boutin and Rapoport *J. Org. Chem.* **1985,** *50*, 3972.

Method 2

Methyl Ester Preparation Procedure

Amino acid methyl esters were prepared using the method of Brenner and Huber *Helv. Chim. Acta* 1953, *36*, 1109.

Method 3

BOP Coupling Procedure

The desired dipeptide ester was prepared by the reaction of a suitable N-protected amino acid (1 equivalent) with the appropriate amino acid ester or amino acid ester hydrochloride (1 equivalent), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate [BOP] (2.0 equivalent), triethylamine (1.1 equivalent), and DMF. The reaction

mixture was stirred at room temperature overnight. The crude product is purified flash chromatography to afford the dipeptide ester.

Method 4

Hydrogenation Procedure I

Hydrogenation was performed using 10% palladium on carbon (10% by weight) in methanol at 30 psi overnight. The mixture was filtered through a pad of Celite and the filtrate concentrated to yield the desired amino compound.

Method 5

Hydrolysis Procedure I

To a chilled (0°C) THF/H_2O solution (2:1, 5 - 10 mL) of the appropriate ester was added LiOH (or NaOH) (0.95 equivalents). The temperature was maintained at 0°C and the reaction was complete in 1-3 hours. The reaction mixture was extracted with ethyl acetate and the aqueous phase was lyophilized resulting in the desired carboxylate salt.

Method 6

Ester Hydrolysis Procedure II

To a chilled (0°C) THF/H_2O solution (2:1, 5 - 10 mL) of the appropriate ester was added LiOH (1.1 equivalents). The temperature was maintained at 0°C and the reaction was complete in 1-3 hours. The reaction mixture was concentrated and the residue was taken up into H_2O and the pH adjusted to 2-3 with aqueous HCl. The product was extracted with ethyl acetate and the combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the desired acid.

Method 7

Ester Hydrolysis Procedure III

The appropriate ester was dissolved in dioxane/H_2O (1:1) and 0.9 equivalents of 0.5 N NaOH was added. The reaction was stirred for 3-16 hours and then concentrated. The resulting residue was dissolved in H_2O and extracted with ethyl acetate. The aqueous phase was lyophilized to yield the desired carboxylate sodium salt.

Method 8

Sulfonylation Procedure I

To the appropriately protected aminophenylalanine analog (11.2 mmol), dissolved in methylene chloride (25ml) and cooled to -78°C was added the desired sulfonyl chloride (12 mmol) followed by dropwise addition of pyridine (2 mL). The solution was allowed to warm to room temperature and was stirred for 48 hr. The reaction solution was transferred to a 250 mL separatory funnel with methylene chloride (100 mL) and extracted with 1N HCl (50 mL x 3), brine (50 mL), and water (100 mL). The organic phase was dried ($MgSO_4$) and the solvent concentrated to yield the desired product.

Method 9

Reductive Amination Procedure

Reductive amination of Tos-Pro-p-NH_2-Phe with the appropriate aldehyde was conducted using acetic acid, sodium triacetoxyborohydride, methylene chloride and the combined mixture was stirred at room temperature overnight. The crude product was purified by flash chromatography.

Method 10

BOC Removal Procedure

Anhydrous hydrochloride (HCl) gas was bubbled through a methanolic solution of the appropriate Boc-amino acid ester at 0°C for 15 minutes and the reaction mixture was stirred for three hours. The solution was concentrated to a syrup and dissolved in Et_2O and reconcentrated. This procedure was repeated and the resulting solid was placed under high vacuum overnight.

Method 11

Tert-Butyl Ester Hydrolysis Procedure I

The *tert*-butyl ester was dissolved in CH_2Cl_2 and treated with TFA. The reaction was complete in 1-3 hr at which time the reaction mixture was concentrated and the residue dissolved in H_2O and lyophilized to yield the desired acid.

Method 12

EDC Coupling Procedure I

To a CH_2Cl_2 solution (5-20 mL) of N-(toluene-4-sulfonyl)-L-proline (1 equivalent), the appropriate amino acid ester hydrochloride (1 equivalent), N-methylmorpholine (1.1-2.2 equivalents) and 1-hydroxybenzotriazole (2 equivalents) were mixed, placed in an ice bath and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.1 equivalents) added. The reaction was allowed to rise to room temperature and stirred overnight. The reaction mixture was poured into H_2O and the organic phase was washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$ or Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography.

Method 13

EDC Coupling Procedure II

To a DMF solution (5-20 mL) of the appropriate N-protected amino acid (1 equivalent), the appropriated amino acid ester hydrochloride (1 equivalent), Et_3N (1.1 equivalents) and 1-hydroxybenzotriazole (2 equivalents) were mixed, placed in an ice bath and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.1 equivalents) added. The reaction was allowed to rise to room temperature and stirred overnight. The reaction mixture was partitioned between EtOAc and H_2O and the organic phase washed with 0.2 N citric acid, H_2O, sat. $NaHCO_3$, and brine, then dried ($MgSO_4$ or Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

Method 14

Sulfonylation Procedure II

The appropriate sulfonyl chloride was dissolved in CH_2Cl_2 and placed in an ice bath. L-Pro-L-Phe-OMe •HCl (1 equivalent) and Et_3N (1.1 equivalent) was added and the reaction allowed to warm to room temperature and stirred overnight under an atmosphere of nitrogen. The reaction mixture was concentrated and the residue partitioned between EtOAc and H_2O and the organic phase washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$ or Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography or preparative TLC.

Method 15

Sulfonylation Procedure III

To a solution of L-Pro-L-4-(3-dimethylaminopropyloxy)-Phe-OMe [prepared using the procedure described in Method 10] (1 equivalent) in CH_2Cl_2 was added Et_3N (5 equivalents) followed by the appropriate sulfonyl chloride (1.1 equivalent). The reaction was allowed to warm to

room temperature and stirred overnite under an atmosphere of nitrogen. The mixture was concentrated, dissolved in EtOAc, washed with sat. $NaHCO_3$ and 0.2 N citric acid. The aqueous phase was made basic with solid $NaHCO_3$ and the product extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$ or Na_2SO_4), filtered and concentrated. The crude methyl ester was purified by preparative TLC. The corresponding acid was prepared using the procedure described in Method 7.

Method 16

Hydrogenation Procedure II

To a methanol (10 -15 mL) solution of the azlactone was added NaOAc (1 equivalent) and 10% Pd/C. This mixture was placed on the hydrogenator at 40 psi H_2. After 8 - 16 hours, the reaction mixture was filtered through a pad of Celite and the filtrate concentrated to yield the dehydrodipeptide methyl ester. The ester was dissolved in dioxane/H_2O (5-10 mL), to which was added 0.5 N NaOH (1.05 equivalents). After stirring for 1- 3 hours, the reaction mixture was concentrated and the residue was redissolved in H_2O and washed with EtOAc. The aqueous phase was made acidic with 0.2 N HCl and the product was extracted with EtOAc. The combined organic phase was washed with brine (1 x 5 mL), dried ($MgSO_4$ or Na_2SO_4), filtered and concentrated to yield the acid as approximately a 1:1 mixture of diastereomers.

Method 17

Tert-Butyl Ester Hydrolysis Procedure II

The *tert*-butyl ester was dissolved in CH_2Cl_2 (5 mL) and treated with TFA (5 mL). The reaction was complete in 1-3 hours at which time the reaction mixture was concentrated and the residue dissolved in H_2O and

concentrated. The residue was redissolved in H_2O and lyophilized to yield the desired product.

Example 1

Synthesis of *N*-(Toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine

N-(Toluene-4-sulfonyl)-2S-indoline-2-carboxylic acid (331.2 mg, 1.04 mmol) was dissolved in dry DMF (5 mL) with 4-methyl morpholine (3.5 eq, 400 μL), BOP (1.1 eq, 506 mg), and phenylalanine benzyl ester (1.0 eq, 444 mg). The dipeptide was isolated as an oil. The benzyl ester was dissolved in EtOH:H_2O (1:1) [2.5 mL] containing a catalytic amount of 10% Pd on C and hydrogenated under 50 psi H_2. Upon filtration over celite, and evaporation of the solvents under reduced pressure the title material was isolated as a solid, mp = 167-170°C.

NMR data was as follows:

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, 1H, J = 8.50 Hz), 7.43 (d, 2H, J = 8.25 Hz), 7.23 (m, 2H), 7.12-7.00 (m, 6H), 6.86 (m, 2H), 4.82 (m, 1H), 4.60 (m, 1H), 3.12 (m, 3H), 2.62 (m, 1H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, CD_3OD): δ = 174.37, 173.24, 146.90, 142.92, 138.09, 136.61, 133.74, 131.49, 130.92, 129.90, 129.49, 129.13, 128.22, 127.37, 126.78, 119.34, 65.28, 55.44, 38.74, 34.15, 22.03.

Mass Spectroscopy: (FAB) 465 (M+H).

Example 2

Synthesis of *N*-(Toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-phenylalanine

Following the experimental procedure described for the synthesis of Example 1 (20), affords the title compound as a white solid, mp = 74-78°C.

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (m, 3H), 7.24-6.85 (m, 10 H), 4.65 (m, 1H), 4.55 (m, 1H), 4.22 (d, 1H, J = 10.5 Hz), 4.05 (d, 1H, J = 10.5 Hz), 3.18-2.92 (m, 4H), 2.34 (s, 3H).

^{13}C NMR (75 MHz, CD_3OD): δ = 174.62, 173.36, 146.96, 138.63, 136.89, 134.17, 131.34, 131.03, 130.12, 129.62, 129.25, 128.87, 128.23, 127.74, 57.59, 56.83, 47.14, 38.75, 31.72, 32.00.

Mass Spectroscopy: (FAB) 479 (M+H).

Example 3

Synthesis of
***N*-(Toluene-4-sulfonyl)glycyl-L-phenylalanine**

N-(Toluene-4-sulfonyl)glycine (547 mg, 2.40 mmol) was slurried in CH_2Cl_2 (7 mL) and cooled in an ice bath. Oxalyl chloride (0.30 mL) was added, followed by one drop of DMF. The mixture was warmed to room temperature and stirred for 1 hr. The volatiles were removed in vacuo and the acid chloride dissolved in CH_2Cl_2 (8 mL) and cooled in an ice bath. Phenylalanine benzyl ester toluensulfonate (919 mg, 2.1 mmol) was added, followed by triethylamine (0.75 mL). The mixture was allowed to slowly warm to room temperature and stirred for 19 hr. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with 1N HCl (2 x 10 mL), 1M $NaHCO_3$ (15 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by silica gel flash chromatography (3:2 Hexane/EtOAc) to give the dipeptide benzyl ester (0.51g, 50%). The benzyl ester was dissolved in THF (20 mL) and 10% Pd/C (60 mg) was added. The mixture was hydrogenated at 15 psi H_2 for 1.5 hr. The mixture was filtered through a pad of diatomaceous earth and evaporated in vacuo to give a residue which was recrystallized from MeOH/$CHCl_3$ to give the title compound as a white solid (304 mg, 76%), mp = 157-161°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$): δ = 12.8 (bs, 1H), 8.13 (d, 1H, J = 8.0 Hz), 7.86 (d, 1H, J = 6.1 Hz), 7.65 (d, 2 H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 7.29-7.17 (5H), 4.49 (m, 1H), 3.01 (dd, 1H, J = 5.0, 13.7 Hz), 3.57 (m, 3H), 2.85 (dd, 1H, J = 8.5, 13.7 Hz), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 172.9, 167.7, 143.0, 137.7, 137.6, 129.9, 129.5, 128.6, 127.0, 53.7, 45.3, 37.2, 21.4.

Mass Spectroscopy: FAB m/e 377 (M+H).

Example 4

Synthesis of *N*-(Toluene-4-sulfonyl)sarcosyl-L-phenylalanine

The product from Example 21 (180) (0.62 mmoles) was added to ethanol (40 mL) and 5% Pd-C (10%) and shaken under 35 psi hydrogen for 16 hours. The reaction mixture was filtered through celite and concentrated. The crude product was crystallized from EtOAc/Hexane to afford the title compound as a white solid (190 mg, 78.5%), mp = 128-130°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.65 (d, 2H, *J* = 8.18 Hz); 7.26 (m, 7H); 4.84 (m, 1H); 3.73 (q, 1H, *J* = 7.02); 3.58 (d, 1H, *J* = 4.28 Hz); 3.20 (m, 2H); 2.55 (s, 3H); 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 175.23, 168.75, 144.90, 136.50, 133.53, 130.57, 129.89, 129.34, 128.17, 127.75, 54.39, 53.84, 37.82, 37.18, 22.15.

Mass Spectroscopy: (+FAB) 391 (M+H), 413 (M+Na).

Example 5

Synthesis of
***N*-(Toluene-4-sulfonyl)-L-alanyl-L-phenylalanine**

The title compound was prepared according to the procedure described in Example 4 (41). The crude product was crystallized from Et_2O/Hexane to yield a white solid, mp = 105 -108°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.72 (d, 2H, J = 8.06 Hz); 7.26 (m, 6H), 7.09 (d, 2H, 7.63 Hz); 6.84 (d, 1H, J = 7.69 Hz); 5.46 (d, 1H, J = 7.70 Hz); 4.71 (m, 1H); 3.77 (m, 2H); 3.09 (m, 2H); 2.41 (s, 3H); 1.14 (d, 3H, J = 7.14 Hz).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 174.60, 172.17, 144.69, 136.79, 136.19, 130.47, 129.93, 129.26, 129.20, 127.80, 127.72, 53.94, 53.05, 37.74, 22.17, 19.71.

Mass Spectroscopy: (+FAB) 391 (M+H), 413 (M+Na).

Example 6

Synthesis of
***N*-(2-Methoxycarbonylbenzenesulfonyl)-glycyl-L-phenylalanine**

The title compound was prepared according to the procedure described for Example 4 (41), yielding a white solid, mp = 140-143°C.

NMR data was as follows:

^{1}H NMR (CD_3OD, 300 MHz): δ = 7.75 (m, 2H); 7.50 (m, 2H); 7.02 (m, 5H); 4.32 (m, 1H); 3.74 (s, 3H); 3.44 (d, 2H, J = 7.57 Hz); 2.91 (m, 1H); 2.72 (m, 1H).

^{13}C NMR (CD_3OD, 300 MHz): δ = 170.66, 169.90, 140.00, 138.73, 134.49, 133.15, 131.96, 131.05, 130.95, 130.92, 130.01, 129.96, 128.35, 55.79, 54.29, 46.98, 38.08, 31.23.

Mass Spectroscopy: (+FAB) 421 (M+H), 443 (M+Na).

Example 7

Synthesis of *N*-(2-Methoxycarbonylbenzenesulfonyl)-L-alanyl-L-phenylalanine

The title compound was prepared according to the procedure described in Example 4 (41), yielding a glassy semi-solid.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.02 (d, 1H, J = 7.14 Hz); 7.84 (d, 1H, J = 7.15 Hz); 7.62 (m, 2H); 7.20 (m, 6H); 6.50 (d, 1H, J = 6.59 Hz); 4.71 (m, 1H); 3.98 (s, 3H); 3.87 (m, 1H); 3.10 (m, 2H); 1.14 (d, 3H, J = 7.14 Hz).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 175.08, 172.26, 168.58, 138.99, 136.47, 133.47, 132.58, 131.63, 130.78, 130.51, 129.95, 129.15, 127.65, 54.12, 54.01, 53.68, 37.93, 19.23.

Mass Spectroscopy: (+FAB) 435 (M+H).

Preparative Example A

Synthesis of *N*-(Saccharin-2-yl)-glycyl-L-phenylalanine

To L-prolyl-L-phenylalanine benzyl ester (4.64 mmoles) in THF (15 mL) was added triethylamine (4.70 mmoles) and the reaction proceeded for 30 minutes at room temperature. The reaction mixture was chilled to 0°C and methyl 2-(chlorosulfonyl) benzoate (4.64 mmoles) was added and the reaction proceeded for 4 hours at room temperature. The reaction was extracted with EtOAc (3 x 50 mL) and water (50 mL), and the combined organic layers were successively washed with sat. $NaHCO_3$ (50 mL) and sat NaCl (2 x 50 mL), dried over $MgSO_4$, filtered and rotovaped to yield a colorless oil (2.30 g, 90%). The crude product was purified by silica gel chromatography (50% EtOAc/Hexane, Rf = 0.47) to yield *N*-(2-Methoxycarbonylphenylsulfonyl)-L-prolyl-L-phenylalanine benzyl ester as

a colorless oil (1.49 g, 58%).

Sodium hydride (1.47 mmoles, washed free of mineral oil) in THF (10 mL) was chilled to 0°C, and a solution of *N*-(2-methoxycarbonylphenyl)sulfonyl-L-glycine-L-phenylalanine benzyl ester in THF (5 mL) was added dropwise. The reaction was stirred at 0°C for one hour and then at room temperature for two hours. The reaction mixture was extracted with EtOAc (3 x 100 mL) and 0.2 N HCl (50 mL), the combined EtOAc layers were washed successively with 0.2 N HCl (50 mL), satd. $NaHCO_3$ (50 mL), and satd. NaCl (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to yield a colorless oil (0.63 g, 91%). The crude product was filtered by silica gel chromatography (50% EtOAc/Hexanes, R_f = 0.42) to afford *N*-(benzisothiazolone)-L-glycyl-L-phenylalanine benzyl ester as a colorless oil (0.25 g, 36%) which was then hydrogenated with 10% Pd on C in THF and the mixture was shaken under 50 psi H_2. The mixture was filtered through celite and evaporated to provide the title compound as a white solid (42 mg, 52%), mp = 201-204°C.

NMR data was as follows:

^1H NMR (CD_3OD, 300 MHz): δ = 7.80 (m, 4H); 7.01 (m, 5H); 4.43 (t, 1H, J = 5.43 Hz); 4.17 (d, 2H, J = 5.43); 2.99 (m, 1H); 2.82 (m, 1H).

^{13}C NMR (CD_3OD, 300 MHz): δ = 167.94, 160.99, 139.70, 138.87, 137.10, 136.46, 131.11, 129.89, 129.01, 128.21, 126.77, 122.87, 56.57, 41.57, 39.04.

Mass Spectroscopy: (+FAB) 398 (M+H), 411 (M+Na).

Example 8

Synthesis of
***N*-(Saccharin-2-yl)-L-**
alanyl-L-phenylalanine

The title compond was prepared using the procedures described for the preparation of Preparative Example A (48), yielding a white solid, mp = 190-193°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$; 300 MHz): δ = 7.86 & 6.95 (m, 9H); 4.66(bs, 2H); 3.18 (m,1H); 2.97 (m, 1H); 1.69 (d, 3H, J = 6.59).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 176.31, 169.18, 158.14, 138.01, 136.68, 135.86, 129.77, 128.81, 127.27, 127.21, 126.13, 121.68, 112.01, 66.48, 54.99, 51.80, 37.53, 14.65.

Mass Spectroscopy: (+FAB) 403 (M+H), 425 (M+Na).

Example 9

Synthesis of
***N*-(Toluene-4-sulfonyl)-**
D,L-phenylglycyl-L-phenylalanine

N-(Toluene-4-sulfonyl)phenylglycine was prepared from phenylglycine using the procedure described in Method 1.

N-(Toluene-4-sulfonyl)phenylglycine-OH and L-Phe-OBn·HCl were treated with BOP and NMM in DMF, to give after aqueous workup and flash chromatography, N-(Toluene-4-sulfonyl)phenylglycine-L-Phe-OBn. This product was treated with 10% Pd on C in THF, and the mixture was shaken under 50 psi H_2. The mixture was filtered through Celite, and evaporated to give the title compound as a solid, mp = 150-152°C.

NMR data was as follows:

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.30 (s, 3H), 2.70-2.95 (m, 2H), 4.13-4.30 (m, 1H), 5.03-5.20 (m, 1H), 6.88-7.34 (m, 12H), 7.55 (m, 2H), 8.38-8.67 (m, 2H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 21.3, 37.3, 53.7, 59.6, 126.7, 126.8, 126.87, 126.92, 127.4, 127.6, 128.2, 128.26, 128.35, 128.6, 129.4, 129.5, 137.2, 137.9, 138.8, 142.5, 169.0, 172.8.

Mass Spectroscopy: (FAB+) 453 (M+H).

Example 10

Synthesis of
***N*-(Toluene-4-sulfonyl)-*N*-methyl-L-phenylalanyl-D,L-phenylalanine**

N-Methyl-L-phenylalanine (500 mg, 2.79 mmol) was dissolved in 1N NaOH (6 mL). Dioxane (9 mL)) was added, followed by *p*-toluenesulfonyl chloride (532 mg, 2.79 mmol) and the mixture was vigorously stirred for 1 hr. The volatiles were removed *in vacuo* and the residue was dissolved in water (30 mL) and washed with Et_2O (2 x 30 mL) before making acidic with 1N HCl. The mixture was extracted with $CHCl_3$ (3 x 30 mL) and the extracts were evaporated *in vacuo* to give *N*-(toluene-4-sulfonyl)-*N*-methylphenylalanine as a solid (424 mg, 45%).

N-(Toluene-4-sulfonyl)-*N*-methylphenylalanine was coupled to L-phenylalanine ethyl ester using the procedure described in Method 3 (400 mg, 62%). The title compound was prepared via hydrolysis of the ethyl ester using NaOH in ethanol. Proton and carbon NMR analyis indicated a mixture of diastereomers.

NMR data was as follows:

^1H NMR ($CDCl_3$): δ = 9.15 (bs, 1H), 7.38-6.89 (14H), 4.82 (m, 1H), 4.70 (m, 1H), 3.31-2.95 (3H), 2.81 (s, 1/2 X 3H), 2.55 (s, 1/2 X 3H), 2.50 (m, 1H), 2.37 (s, 1/2 X 3H), 2.35 (s, 1/2 X 3H).

^{13}C NMR ($CDCl_3$): δ = 175.3, 169.6, 169.5, 143.5, 143.4, 137.0, 136.9, 135.6, 135.5, 135.3, 135.2, 129.8, 129.7, 129.6, 129.3, 129.2, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 127.2, 127.1, 127.0, 126.6,

126.4, 124.8, 61.2, 61.0, 53.5, 53.4, 37.4, 37.1, 33.9, 33.5, 29.9, 29.6, 21.4.

Mass Spectroscopy: FAB m/e 481 (M+H).

Example 11

Synthesis of *N*-(Toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine

Boc-L-Diphenylalanine was coupled to L-phenylalanine benzyl ester using the procedure described in Method 3. The Boc group was removed by treatment with TFA and anisole, and the mixture was evaporated. The residue was dissolved in Et_2O and washed with sat. $NaHCO_3$ and sat. NaCl. The Et_2O layers were dried with $MgSO_4$, filtered, and evaporated to give the deprotected dipeptide. The resulting ester of the title compound was tosylated using the procedure described in Method 1. The title compound was prepared using the procedure described in Method 7 as a solid, mp = 228-230°C.

NMR data was as follows:

^1H NMR (CD_3OD, 300 MHz): δ = 2.11 (s, 3H), 2.37-2.46 (m, 2H), 3.78 (m, 1H), 3.99 (d, 1H, J = 10.8 Hz), 4.49 (d, 1H, J = 10.8 Hz), 6.86-7.04 (m, 17H), 7.36 (d, 2H, J = 8.3 Hz).

^{13}C NMR (CD_3OD, 75 MHz): δ = 22.0, 39.8, 56.1, 56.3, 61.6, 128.09, 128.14, 128.4, 128.7, 128.8, 129.8, 129.9, 130.0, 130.1, 130.3, 131.07, 131.11, 138.7, 140.0, 142.2, 142.4, 144.9, 172.3, 174.5.

Mass Spectroscopy: (FAB+) 549 (M+ Li).

Example 12

Synthesis of *N*-(Toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine

N-(Toluene-4-sulfonyl)sarcosine was prepared from sarcosine using the procedure described in Method 1. Coupling was conducted using the procedure described in Method 3. The title compound, prepared by hydrolysis of the ester using the procedure described in Method 7, was obtained as a solid, mp = >200°C (dec.).

NMR data was as follows:

^{1}H NMR (D_2O, 300 MHz): δ = 2.17 (s, 3H), 2.28 (s, 3H), 2.71-3.05 (m, 2H), 3.31-3.48 (dd, 2H), 4.34 (m, 1H), 6.74 (s, 1H), 6.97-7.16 (m, 7H), 7.37 (d, 2H, J = 8.0 Hz), 7.44 (s, 1H).

^{13}C NMR (D_2O, 75 MHz): δ = 27.7, 37.2, 43.0, 57.3, 59.8, 61.7, 124.7, 134.3, 134.6, 134.9, 135.8, 137.0, 138.9, 143.7, 144.2, 144.3, 152.0, 176.0, 184.6.

Mass Spectroscopy: (FAB+) 493 (M+H).

Example 13

Synthesis of *N*-(Toluene-4-sulfonyl)sarcosyl-D,L-β-(3-pyridyl)alanine

Sodium metal (1.40 g, 61 mmol) was dissolved in EtOH (100 mL) containing diethyl acetamidomalonate (6.62 g, 30.5 mmol) and 3-picolyl chloride hydrochloride (5.00 g, 30.5 mmol) were added. The mixture was heated to reflux for 6 hr, and then cooled and filtered to remove NaCl (washed with EtOH). The solvent was removed *in vacuo* and the mixture was taken up into saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 x 100 mL). The solvent was removed and the residue purified

by silica gel flash chromatography (95:5 CH_2Cl_2/MeOH) to give diethyl 2-(3-pyridylmethyl)-2-acetamidomalonate (2.84 g, 30%).

Diethyl 2-(3-pyridylmethyl)-2-acetamidomalonate was dissolved in 6N HCl (30 mL) and heated to reflux for 19 hr whereupon it was cooled to room temperature and the HCl solution was removed by evaporation *in vacuo*. The intermediate amino acid dihydrochloride salt was taken up into MeOH (30 mL) saturated with HCl gas and stirred for 3.5 hr. The MeOH/HCl was removed by evaporation *in vacuo* to give β-(3-pyridyl)alanine methyl ester dihydrochloride (2.235 g, 100%).

N-(Toluene-4-sulfonyl)sarcosine was coupled to 3-(3-pyridyl)alanine methyl ester dihydrochloride using the procedure described in Method 3 to give *N*-(toluene-4-sulfonyl)sarcosyl-β-(3-pyridyl)alanine (166 mg, 17%). The title compound was prepared via hydrolysis of the methyl ester using 1N aqueous NaOH in dioxane/water (129 mg, 100%).

NMR data was as follows:

^1H NMR (DMSO-d_6): δ = 8.30 (m, 2H), 7.66 (d, 2H, J = 8.0 Hz), 7.63 (m, 1H), 7.51 (m, 1H), 7.42 (d, 2H, J = 7.9 Hz), 7.20 (m, 1H), 4.07 (m, 1H), 3.56 (s, 2H), 3.11 (dd, 1H, J = 4.8, 13.2 Hz), 2,96 (dd, 1H, J = 5.5, 13.4 Hz), 2.52 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 172.7, 166.0, 150.8, 147.3, 143.8, 137.3, 134.8, 134.0, 130.2, 127.7, 123.3, 55.3, 53.2, 36.2, 34.9, 21.4.

Mass Spectroscopy: FAB m/e 392 (M+H).

Example 14

Synthesis of
***N*-(Toluene-4-sulfonyl)sarcosyl-**
D,L-β-(4-pyridyl)alanine

The title compound was prepared as described in Example 13 (107) except 4-picolylchloride hydrochloride is used in place of 3-picolylchloride hydrochloride.

NMR data was as follows:

^{1}H NMR (CD_3OD): δ = 8.39 (d, 2H, *J* = 5.3 Hz),7.68 (d, 2H, *J* = 8.2 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 5.8 Hz), 4.58 (m, 1H), 3.70 (d, 1H, *J* = 16.6 Hz), 3.54 (d, 1H, *J* = 16.5 Hz), 3.30 (dd, 1H, *J* = 4.9, 13.7 Hz), 3.07 (dd, 2H, *J* = 7.6, 13.7 Hz), 2.66 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (CD_3OD): δ = 176.0, 270.2, 150.8, 150.1, 146.1, 135.7, 131.5, 129.3, 127.4, 56.4, 54.8, 39.1, 37.6, 22.1.

Mass Spectroscopy: FAB m/e 392 (M+H).

Example 15

Synthesis of
***N*-(Toluene-4-sulfonyl)sarcosyl-L-**
β-(2-pyridyl)alanine

N-(Toluene-4-sulfonyl)sarcosine was coupled to L-β-(2-pyridyl)alanine methyl ester dihydrochloride using the procedure described in Method 3 to give *N*-(toluene-4-sulfonyl)sarcosyl-β-(2-pyridyl)alanine methyl ester. The title compound was prepared via hydrolysis of the methyl ester using 1N aqueous NaOH in dioxane/water.

NMR data was as follows:

^{1}H NMR (DMSO-d_6): δ = 8.38 (m. 1H),7.72 (d, 1H, *J* = 7.4 Hz), 7.65 (d, 2H, *J* = 8.2 Hz), 7.59 (m, 1H), 7.41 (d, 2H, *J* = 8.2 Hz), 7.21 (d, 1H, *J* = 7.8 Hz), 7.12 (m 1H), 4.23 (m, 1H), 3.50 (m, 2H), 3.23 (dd,

1H, J = 4.8, 13.4 Hz), 3.01 (dd, 2H, J = 7.1, 13.4 Hz), 2.53 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (DMSO-d_6): δ = 173.4, 165.7, 159.7, 148.9, 243.8, 136.1, 134.0, 130.2, 127.7, 124.0, 121.4, 54.7, 53.3, 36.1, 21.4.

Mass Spectroscopy: FAB m/e 414 (M+Na).

Example 16

Synthesis of
***N*-(Toluene-4-sulfonyl)-**
D,L-phenylsarcosyl-L-phenylalanine

N-(Toluene-4-sulfonyl)phenylsarcosine was prepared from phenylsarcosine using the procedure described in Method 1. The title compound was prepared using the procedure described for Example 9 (65) as a solid, mp = 78-82°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.41 (s, 3H), 2.48 (s, 3H), 2.97-3.34 (m, 2H), 4.89 (m, 1H), 5.63 (s, 1H), 6.77-6.92 (m, 3H), 7.13-7.35 (m, 10H), 7.66 (d, 2H, J = 7.5 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.2, 32.3, 38.0, 53.9, 64.4, 127.8, 128.1, 129.1, 129.4, 129.88, 129.95, 130.0, 130.3, 133.9, 136.2, 136.4, 144.4, 169.8, 175.2.

Mass Spectroscopy: (FAB+) 467 (M+H).

Preparative Example B

Synthesis of
***N*-(Toluene-4-sulfonyl)sarcosyl-**
***N*-methyl-L-phenylalanine**

N-(Toluene-4-sulfonyl)sarcosine was coupled to *N*-methyl-L-phenylalanine methyl ester using the procedure described in Method 3 to give *N*-(toluene-4-sulfonyl)sarcosyl-*N*-methylphenylalanine methyl ester.

The title compound was prepared via hydrolysis of the methyl ester using LiOH in THF/water. Proton and carbon NMR analysis indicated a mixture of amide bond rotomers in about a 65:35 ratio.

NMR data was as follows:

^{1}H NMR ($CDCl_3$): δ = 7.59 (d, 0.65 x 2H, J = 7.4 Hz), 7.54 (d, 0.35 x 2H, J = 7.3 Hz), 7.34-7.18 (7H), 5.25 (m, 0.65H), 5.09 (m, 0.35H), 3.93 (d, 0.65H, J = 14.6 Hz), 3.58 (d, 0.65H, J = 14.6 H), 3.41 (m, 1H), 3.10 (m, 1H), 2.97 (s, 0.65 x 3H), 2.92 (s, 0.35 x 3H), 2.41 (s, 3H), 2.39 (s, 0.65 x 3H), 2.38 (s, 0.35 x 3H).

^{13}C NMR ($CDCl_3$): δ = 173.3, 168.1, 167.8, 143.9, 143.8, 136.9, 136.8, 133.3, 129.7, 129.1, 128.8, 128.7, 128.6, 127.5, 127.0, 126.8, 59.0, 52.8, 52.7, 35.0, 34.7, 34.2, 33.0, 30.1, 21.5.

Mass Spectroscopy: FAB m/e 405 (M+H).

Example 17

Synthesis of
N-(Toluene-4-sulfonyl)-L-aspartyl-L-phenylalanine

Cbz-4-(1,1-dimethylethyl)aspartic acid was coupled with phenylalanine t-butyl ester using the procedure described in Method 3. The Cbz group was removed using the procedure described in Method 4. The resulting ester was tosylated using the procedure described in Method 1. The title compound was prepared using the procedure outlined in Method 11.

NMR data was as follows:

^{1}H NMR (CD_3OD, 300 MHz): δ = 2.18 (s, 3H), 2.18-2.39 (m, 2H), 2.68-2.89 (m, 2H), 3.97 (t, 1H, J = 5.2 Hz), 4.22 (t, 1H, J = 4.9 Hz), 6.97-7.12 (m, 7H), 7.45 (d, 2H, J = 8.2 Hz).

^{13}C NMR (CD_3OD), 75 MHz): δ = 22.1, 38.6, 38.9, 55.1, 55.9, 128.5, 128.8, 130.1, 130.9, 131.0, 131.3, 138.3, 138.6, 139.4, 145.5, 172.6.

Mass Spectroscopy: (FAB+) 435 (M+H).

Example 18

Synthesis of N-(Toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinolin-3-carbonyl)-L-phenylalanine Benzyl Ester

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroquinolin-3-carbonyl) (1 eq) was dissolved in DMF, with Et_3N (2.0 eq), BOP (1.1 eq), and L-phenylalanine benzyl ester·HCl salt (1.1 eq). The benzyl ester was isolated as an oil.

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, 2H, J = 8.16 Hz), 7.33 (m, 5H), 7.23-7.08 (m, 8H), 6.70 (d, 2H, J = 8.16 Hz), 5.10 (q, 2H, J = 11.50 Hz), 4.72 (m, 1H), 4.52 (m, 1H), 4.18 (m, 2H), 3.07 (m, 2H), 2.85 (m, 2H), 2.52 (m, 1H), 2.34 (s, 3H).

Example 19

Synthesis of N-(Toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine Benzyl Ester

The procedure used for the preparation of Example 18 (173) was utilized. The title compound was isolated as an oil.

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, 1H, J = 7.98 Hz), 7.42-6.92 (m, 16H), 6.66 (d, 2H, J = 8.50 Hz), 5.17 (q, 2H, J = 10.08 Hz), 4.83 (m, 1H), 4,58 (m, 1H), 3.07 (m, 3H), 2.62 (m, 1H), 2.32 (s, 3H).

Example 20

Synthesis of
***N*-(Toluene-4-sulfonyl)-L-alanyl-**
L-phenylalanine Benzyl Ester

To *N*-(toluene-4-sulfonyl)-L-alanine (2.0 mmoles) in DMF (10 mL) was added BOP (2.1 mmoles) and *N*-methylmorpholine (4.0 mmoles) and the reaction stirred at room temperature for 45 minutes. L-Phenylalanine benzyl ester (2.0 mmoles) was added and the reaction stirred for 16 hours at room temperature. The reaction mixture was extracted with water (100 mL) and diethyl ether (3 x 50 mL) The combined organic layers were successively washed with 0.2 N HCl (2 x 50 mL), sat. $NaHCO_3$ (50 mL), and sat. NaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield a colorless oil (387 mg, 40%). The crude product was purified by silica gel chromatography (50% EtOAc /Hexane, Rf = 0.61). The title compound was crystalized from $CHCl_3$/Hexane to yield a white solid, mp = 109-110°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.75 (d, 2H, J = 8.24 Hz); 7.26 (m, 13H); 5.88 (d, 1H, J = 7.69 Hz); 5.11 (q, 2H, J = 12.1 Hz); 4.76 (q, 1H, J = 7.69 Hz); 3.85 (m, 1H); 3.00 (d, 2H, J = 5.98 Hz); 2.37 (s, 3H); 1.19 (d, 3H, J = 7.09 Hz).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 171.83, 171.49, 144.30, 137.34, 136.12, 135.53, 130.36, 130.00, 129.90, 129.19, 129.12, 127.85, 127.71, 127.65, 67.92, 54.07, 52.94, 38.26, 22.13, 19.96.

Mass Spectroscopy: (+FAB) 481 (M+H).

Example 21

Synthesis of *N*-(Toluene-4-sulfonyl)sarcosyl-L-phenylalanine Benzyl Ester

The title compound was prepared according to Method 3, and the crude product was crystallized from Et_2O/hexane to afford a white solid, mp = 80-82°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64 (d, 2H, J = 8.24 Hz); 7.26 (m, 13H); 5.16 (q, 2H, J = 12.1 Hz); 4.92 (d of t, 1H, J = 6.71 & 11.29 Hz); 3.7.70 (d, 1H, J = 16.48 Hz); 3.43 (d, 1H, J = 16.48 Hz); 3.15 (m, 2H); 2.56 (s, 3H); 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 171.34, 167.88, 144.88, 135.97, 135.60, 133.61, 130.56, 129.85, 129.36, 129.22, 129.15, 128.16, 127.84, 67.93, 54.51, 53.51, 38.29, 37.15, 22.16.

Mass Spectroscopy: (+FAB) 481 (M+H).

Example 22

Synthesis of *N*-(Toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine Ethyl Ester

N-(Toluene-4-sulfonyl)phenylglycine was prepared from phenylglycine using the procedure described in Method 1. The title compound was prepared using the procedure described for Example 11 (86) as a solid, mp = 145-147°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.12-1.29 (m, 3H), 2.38 (s, 3H), 2.91-3.05 (m, 2H), 4.04-4.20 (m, 2H), 4.65-4.81 (m, 2H), 5.85-5.95 (m, 1H), 6.07-6.21 (m, 1H), 6.65 (m, 1H), 6.95 (m, 1H), 7.02-7.33 (m, 10H), 7.60 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = (diastereomeric pairs separated by slashed line) 14.57/14.70, 22.09/22.10, 38.1, 53.7/54.2, 61.00/61.06, 62.26/62.34, 127.61/127.76, 127.81/127.88, 128.06/128.16, 129.06/129.16, 129.3, 129.6, 129.69/129.76, 130.06/130.08, 135.4, 136.01/136.55, 136.94/137.21, 144.03/144.13, 168.67/169.00, 171.07/171.22.

Mass Spectroscopy: (FAB+) 481 (M+H).

Example 23

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)-seryl-L-phenylalanine Ethyl Ester

L-(*O*-Benzyl)-serine methyl ester hydrochloride salt (6.28 g, 25.5 mmol) was dissolved in dichloromethane (50 mL) with tosyl chloride (1.1 eq, 5.36 g) and Et_3N (2.2 eq, 7.48 mL). The reaction mixture was stirred at room temperature for 12 hours. The solvent was evaporated under reduced pressure. EtOAc was added as well as brine, and the organic layer dried over $MgSO_4$. The desired *N*-(toluene-4-sulfonyl)-L-(*O*-benzyl)-serine methyl ester was isolated as an oil, in 100% yield (10.04 g, 25.5 mmol). This was then taken up in dry acetone (50 mL) with iodomethane (1.1 eq, 1.88 mL) and K_2CO_3 (1.1 eq, 4.10 g). The solution was refluxed overnight. The solvent was evaporated under reduced pressure. EtOAc was added and the organic layer was washed with brine. The organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The desired *N*-methyl derivative was isolated as a clear oil in 40% yield (4.16 g, 11 mmol). The ester was dissolved in a 1:1 solution of dioxane:H_2O with NaOH (1.1 eq, 50 mL). The desired compound was isolated as a solid.

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)serine (754 mg, 2.07 mmol) was dissolved in 30 mL of dry DMF with phenylalanine ethyl ester hydrochloride salt (1.1 eq, 525 mg), Et_3N (2.2 eq, 636 mL) and BOP reagent (1.1 eq, 1.00 g). The reaction mixture was stirred at room temperature for 12 hours. EtOAc was added. The organic layer was washed with $NaHCO_3$ saturated, 10% citric acid, and brine. The organic layer was dried over $MgSO_4$. Upon evaporation of the solvents under reduced pressure, the crude material was eluted on column chromatography (Silica gel; $CHCl_3$/MeOH 9:1). The title ester was isolated as an oil in 60% yield (664 mg, 1.23 mmol) and as a mixture of diastereoisomers.

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, 2H, J = 8.22 Hz), 7.27 (m, 5H), 7.15 (m, 5H), 7.04 (m, 2H), 4.80 (m, 2H), 4.29 (m, 4H), 3.76 (m, 1H), 3.58 (m, 1H), 3.19 (m, 2H), 2.71 (s, 1.5 H), 2.57 (s, 1.5H), 2.35 (s, 3H), 1.27 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.50, 168.70, 143.98. 137.84, 136.44, 136.18, 129.93, 128.98, 128.45, 128.37, 128.25, 127.65, 73.75, 67.15, 66.99, 62.17, 60.35, 59.98, 53.93, 53.75, 38.34, 30.95, 22.15, 14.69.

Mass Spectroscopy: (FAB) 539 (M+H).

Example 24

Synthesis of
***N*-(Toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-phenylalanine Ethyl Ester**

Example 23 (191) (664 mg, 1.23 mmol) was dissolved in MeOH (10 mL) with a catalytic amount of Pearlman's catalyst. The hydrogenation reaction was run for 2 hours at 5 psi. The solution was filtered over celite. Upon evaporation of the solvent under reduced pressure, an oil was isolated as the title compound in quantitative yields.

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (m, 2H), 7.30 (m, 7H), 4.77 (m, 1H), 4.46 (m, 1H), 4.18 (m, 2H), 3.65 (m, 1H), 3.47 (m, 2H), 3.07 (m, 2H), 2.78 (s, 1.5H), 2.54 (s, 1.5H), 2.42 (s, 3H), 1.25 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.47, 170.31, 144.78, 136.42, 135.77, 130.67, 129.88, 129.33, 127.92, 127.80, 62.44, 60.99, 60.81, 54.00, 53.77, 38.32, 32.19, 31.96, 22.24, 14.76.

Mass Spectroscopy: (FAB) 449 (M+H).

Example 25

Synthesis of *N*-(Toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine Benzyl Ester

Boc-L-diphenylalanine was coupled to L-phenylalanine benzyl ester using the procedure described in Method 3. The Boc group was removed using the procedure described in Example 11 (86). The resulting ester was tosylated using the procedure described in Method 1 yielding the title compound as a solid, mp = 79-84°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.36 (s, 3H), 2.77 (m, 2H), 4.25-4.39 (m, 2H), 4.95 (d, 2H, J = 4.9 Hz), 5.19 (d, 1H, J = 8.0 Hz), 6.18 (d, 1H, J = 7.8 Hz), 6.92 (m, 2H), 7.08-7.38 (m, 20H), 7.55 (d, 2H, J = 8.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1, 38.8, 54.1, 54.7, 60.9, 67.7, 127.6, 127.70, 127.72, 128.0, 128.7, 129.10, 129.14, 129.3, 129.9, 130.2, 135.5, 136.0, 137.0, 139.4, 140.1, 144.2, 169.9, 170.8.

Mass Spectroscopy: (FAB+) 633 (M+H).

Example 26

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine Ethyl Ester

N-(Toluene-4-sulfonyl)phenylglycine was esterified with thionyl chloride in methanol to give *N*-(toluene-4-sulfonyl)phenylglycine methyl ester. This was then taken up in dry acetone (50 mL) with iodomethane (1.1 eq, 1.88 mL) and K_2CO_3 (1.1 eq, 4.10 g). The solution was refluxed overnight. The solvent was evaporated under reduced pressure. EtOAc was added and the organic layer was washed with brine. The organic layer was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The resulting ester was hydrolyzed using the procedure described in Method 6 to yield *N*-(Toluene-4-sulfonyl)-*N*-methyl-phenylglycine, which was coupled with L-phenylalanine ethyl ester using the procedure described in Method 3 to yield the title compound.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.27 (t, 3H), 2.43 (s, 3H), 2.60 (s, 3H), 2.98-3.25 (m, 2H), 4.21 (q, 2H), 4.80-4.91 (m, 1H), 5.68 (s, 1H), 6.59 (br d, minor dia., 1H with 6.73) 6.73 (br d, major dia., 1H with 6.59), 6.92-7.02 (m, 2H), 7.11-7.43 (m, 10H), 7.69 (d, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = (Major diastereomer) 14.75, 22.16, 32.20, 38.38, 53.56, 62.21, 64.43, 127.79, 128.07, 129.07, 129.13, 129.27, 129.87, 129.92, 130.04, 134.18, 136.10, 136.32, 144.22, 169.08, 171.71; (Minor diastereomer) 14.68, 22.16, 32.12, 38.51, 53.97, 62.21, 64.22, 127.76, 128.16, 129.07, 129.13, 129.32, 129.87, 129.92, 130.26, 134.26, 136.10, 136.52, 144.26, 169.08, 171.71.

Mass Spectroscopy: (FAB+) 495 (M+H).

Example 27

Synthesis of
***N*-(Toluene-4-sulfonyl)sarcosyl-L-**
(*N*-benzyl)histidine Methyl Ester

N-(Toluene-4-sulfonyl)sarcosine methyl ester was prepared from sarcosine methyl ester using the procedure described in Method 1. The title compound was prepared by coupling in DMF N-(toluene-4-sulfonyl)sarcosine with (*N*-benzyl)histidine methyl ester in the presence of BOP and NMM, to give after aqueous workup and flash chromatography, the title compound.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.44 (s, 3H), 2.76 (s, 3H), 3.09 (m, 2H), 3.44 (d, 1H, J = 16.4 Hz), 3.68 (s, 3H), 3.83 (d, 1H, J = 16.5 Hz), 4.80 (m, 1H), 5.07 (s, 2H), 6.74 (s, 1H), 7.14 (d, 2H, J = 6.0 Hz), 7.33 (m, 5H), 7.50 (s, 1H), 7.68 (d, 2H, J = 8.3 Hz), 8.06 (br d, 1H, 8.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.8, 22.1, 30.2, 37.1, 51.4, 52.6, 52.9, 54.4, 61.0, 117.8, 128.0, 128.2, 128.8, 129.6, 130.5, 134.0, 136.6, 137.8, 137.9, 144.6, 168.2, 172.1.

Mass Spectroscopy: (FAB+) 485 (M+H).

Example 28

Synthesis of
***N*-(Toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-**
(*N*-benzyl)histidine Methyl Ester

N-Methyl-*N*-(toluene-4-sulfonyl)-L-serine (420 mg, 1.53 mmol) was dissolved in dry DMF (20 mL) at ice bath temperature. L-(*N*-benzyl)histidine methyl ester hydrochloride salt (1.1 eq, 500 mg) was added as well as Et_3N (2.2 eq, 471 mL), with HOBT (1.1 eq, 229 mg). After 15 mn, EDCI (1.1 eq, 502 mg) was added and the reaction mixture was stirred at room temperature overnight. EtOAc was added and the

organic layer washed with $NaHCO_3$ saturated, 10% citric acid and brine (3x50 mL). The organic layer was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The crude material was eluted on column chromatography (silica gel), with EtOAc/hexanes 1:3, then with $CHCl_3$:MeOH 9:1. The title compound was isolated as an oil in 30% yield (230 mg, 0.447 mmol).

NMR data was as follows:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, 1H, J = 7.50 Hz), 7.73 (d, 2H, J = 8.31 Hz), 7.46 (s, 1H), 7.32 (m, 5H), 7.15 (m, 2H), 6.69 (s, 1H), 5.04 (s, 2H), 4.74 (m, 1H), 4.46 (m, 1H), 3.71 (m, 2H), 3.66 (s, 3H), 3.06 (m, 2H), 2.80 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.98, 170.40, 144.41, 137.93, 136.54, 135.976, 130.41, 129.57, 128.88, 128.01, 117.74, 61.42, 61.15, 53.07, 51.46, 32.29, 30.09, 22.13 (1C missing).

Mass Spectroscopy: (FAB) 515 (M+H).

Example 29

Synthesis of *N*-(Toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine Benzyl Ester

The title compound was prepared by coupling *N*-(toluene-4-sulfonyl)-D,L-phenylglycine to L-phenylalanine benzyl ester using the procedure described in Method 3 to provide a solid, mp = 148-150°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.37 (s, 3H), 2.91-3.07 (m, 2H), 4.70-4.85 (m, 2H), 5.04 (dd, 2H), 5.94 (br d, 1H), 6.23 (br d, 1H), 6.84 (d, 2H), 7.00-7.40 (m, 15H), 7.60 (d, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1, 38.1, 54.2, 61.1, 67.9, 127.7, 127.8, 127.9, 128.1, 128.2, 129.1, 129.4, 129.6, 129.7, 129.8, 130.0, 135.4, 135.8, 136.5, 137.2, 144.1, 169.1, 170.9.

Mass Spectroscopy: (FAB+) 543 (M+H).

Example 30

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine Benzyl Ester

The title compound was prepared following the procedure described in Example 26 (198) as a solid, mp = 46-49°C.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.41 (s, 3H), 2.54, (s, 3H), 2.96-3.22 (m, 2H), 4.90 (q, 1H, J = 3.0 Hz), 5.15 (dd, 2H), 5.65 (s, 1H), 6.51 (d, 1H, J = 6.9 Hz), 6.95 (d, 2H, J = 6.2 Hz), 7.04 (m, 2H), 7.15-7.40 (m, 13H), 7.67 (d, 2H, J = 8.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.2, 32.1, 38.4, 53.9, 64.3, 68.0, 127.8, 128.1, 129.1, 129.2, 129.3, 129.4, 129.8, 129.9, 130.0, 130.1, 130.2, 134.2, 135.6, 136.2, 136.5, 144.2, 169.1, 171.4.

Mass Spectroscopy: (FAB+) 557 (M+H).

Example 31

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-(2-thienylethyl)-glycyl-L-phenylalanine Methyl Ester

N-(Toluene-4-sulfonyl)-2-thienylethylamine was prepared using the procedure described in Method 1. This compound was reacted with t-butyl bromoacetate yielding *N*-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycine t-butyl ester (following the method of Zuckermann, Kerr, Kent, and Moos *J. Am. Chem. Soc.* 1992, *114*, 10646-10647). The ester was hydrolyzed

using the procedure described in Method 17. The title compound was prepared following the procedure described in Method 13.

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.43 (s, 3H), 2.85 (m, 2H), 3.05-3.22 (m, 3H), 3.40 (m, 1H), 3.69 (dd, 2H), 3.73 (s, 3H), 4.83 (m, 1H), 6.73 (d, 1H, J = 2.3 Hz), 6.90 (t, 1H, J = 2.4 Hz), 6.98 (br d, 1H, J = 6.2 Hz), 7.13 (d, 1H, J = 3.2 Hz), 7.17-7.35 (m, 7H), 7.66 (d, 2H, J= 8.0 Hz).

Example 32

Synthesis of
***N*-(Toluene-4-sulfonyl)-*N*-(2-thienylethyl)-glycyl-L-phenylalanine**

The title compound was prepared from the product of Example 31 (289) using the procedure described in Method 7 to provide a solid, mp = >200°C.

Example 33

Synthesis of
***N*-(Toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-(*N*-benzyl)histidine Methyl Ester**

The title compound was prepared according to procedures described in Example 31 (289).

NMR data was as follows:

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.41 (s, 3H), 2.82 (m, 2H), 3.02-3.30 (m, 3H), 3.46 (m, 1H), 3.67 (s, 3H), 3.75 (dd, 2H), 4.79 (m, 1H), 5.00 (s, 2H), 6.77 (s, 1H), 7.10-7.35 (m, 12H), 7.48 (s, 1H), 7.69 (d, 2H, J = 7.3 Hz), 7.97 (br d, 1H, J = 6.9 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1, 30.2, 35.3, 51.4, 52.6, 52.7, 52.9, 118.1, 127.2, 127.9, 128.0, 128.8, 129.2, 129.4, 129.5, 130.5, 135.7, 136.6, 137.6, 137.8, 138.5, 144.6, 168.9, 172.0.

Mass Spectroscopy: (FAB+) 575 (M+H); 597 (M+Na^+).

Example 34

Synthesis of *N*-(Toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-phenylalanine

The title compound was prepared according to procedures described in Examples 31 (289) and 32 (290).

NMR data was as follows:

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.41 (s, 3H), 2.56 (m, 2H), 3.03-3.37 (m, 4H), 3.72 (dd, 2H), 4.84 (q, 1H, J = 3.4 Hz), 7.02 (d, 2H, J = 6.1 Hz), 7.12-7.34 (m, 10H), 7.63 (d, 2H, J = 8.3 Hz), 8.78 (br s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.1, 35.1, 37.8, 52.6, 52.7, 53.8, 127.3, 127.9, 128.0, 129.2, 129.3, 129.4, 130.0, 130.6, 135.2, 136.0, 138.1, 144.9, 169.9, 175.0.

Mass Spectroscopy: (FAB+) 481 (M+H).

Example 35

Synthesis of *N*-(Toluene-4-sulfonyl)sarcosyl-D,L-4-cyanophenylalanine

N-(Toluene-4-sulfonyl)sarcosine was coupled to 4-cyanophenylalanine methyl ester hydrochloride (prepared via the method of Wagner, Voight, and Vieweg *Pharmazie* 1984, *39*, 226-230) to give *N*-(toluene-4-sulfonyl)sarcosyl-D,L-4-cyanophenylalanine methyl ester. The compond was prepared via hydrolysis of the methyl ester using 0.5 N NaOH in THF/water.

NMR data was as follows:

^{1}H NMR ($CD_3OD/CDCl_3$): δ = 7.69 (m, 3H), 7.41 (m, 3H), 4.79 (m, 1H), 3.77 (d, 1H, J = 16.7 Hz), 3.55 (d, 1H, J = 16.5 Hz), 3.32 (dd, 1H, J = 4.9, 14.0 Hz), 3.13 (dd, 1H, J = 8.8, 14.0 Hz), 2.67 (s, 3H), 2.45 (s, 3H).

^{13}C NMR ($CD_3OD/CDCl_3$): δ = 174.0, 170.6, 146.2, 144.9, 135.5, 134.0, 132.2, 131.6, 129.3, 120.4, 112.3, 54.8, 50.4, 39.0, 37.7, 22.4.

Mass Spectroscopy: FAB m/e 416 (M+H).

Example 36

Synthesis of *N*-(Toluene-4-sulfonyl)-L-*tert*-butylglycyl-L-phenylalanine

N-(Toluene-4-sulfonyl)-L-*tert*-butylglycine was prepared from L-*tert*-butylglycine using the procedure described in Method 1. The title compound was prepared by coupling in DMF N-(toluene-4-sulfonyl)-L-*tert*-butylglycine with an L-phenylalanine ester in the presence of BOP and NMM. Conventional deesterification provided the title compound.

NMR data was as follows:

^{1}H NMR ($CDCl_3$): δ 7.7 (d, 2H), 7.25 (m, 5H), 7.0 (m, 2H), 5.93 (d, 1H), 5.57 (d, 1H), 4.6 (m, 1H), 3.3 (d, 1H), 3.0-2.7 (d of d, 2H), 2.35 (s, 3H), 0.87 (s, 9H).

Example 37

Synthesis of *N*-(Saccharin-2-yl)-D,L-alaninyl-L-4-(isonicotinamido)phenylalanine Methyl Ester

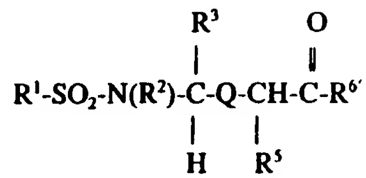
The title compound was prepared following the procedures described in Preparative Example A. *N*-(saccharin-2-yl)-D,L-alaninyl-L-p-amino-phenylalanine methyl ester (1 eq) was dissolved in dichloromethane with

Et_3N (1.1 eq) and reacted with isonicotinoyl chloride (1.1 eq, 860 mL) to provide the title compound.

NMR data was as follows:

^1H NMR (DMSO-d_6,400 MHz) (1:1 mixture of diastereomers): δ = 10.43 (d, 1H); 8.80 (m, 2H); 8.45 and 8.25 (two m, 1H), 8.23 (m, 1H); 8.04 (m, 3H); 7.82 (m, 2H); 7.65 (m, 2H); 7.20 (m, 2H); 4.76 (m, 1H); 4.45 (m, 1H); 3.40 and 3.42 (two s, 3H); 3.00 (m, 2H), 1.65 and 1.70 (two s, 3H).

Other compounds prepared by the methods described above include those set forth in Table II below:



R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7- R^7	Ex. No.
p-CH_3-φ-	-CH_3	L -CH(φ)$_2$	-CH_2-φ	-OH	H	38
p-CH_3-φ-	φ	H	-CH_2-φ	OH	H	39
p-CH_3-φ-	-CH_2φ	H	-CH_2-φ	-OCH_3	H	40
p-CH_3-φ-	-CH_2φ	H	-CH_2-φ	-OH	H	41
p-CH_3-φ-	-CH_3	H	p-[-C≡C-(2-pyridyl)]-benzyl-	-OH	H	42

R^1	R^2	R^3	R^5	$R^{6'}$	Q = -C(O)NR^7-R^7	Ex. No.
p-CH_3-ϕ-	-CH_3	H	*p*-[-C≡C-(*m*-hydroxyphenyl)]-benzyl-	-OH	H	43
p-CH_3-ϕ-	-CH_3	H	*p*-iodobenzyl-	-OH	H	44
ϕ-CH_2-	-CH_3	-CH_2OH (L isomer)	1-N-benzylimidazol-4-yl-CH_2-	-OCH_3	H	45

Example 46

In vitro Assay For Determining Binding of Candidate Compounds to VLA-4

An *in vitro* assay was used to assess binding of candidate compounds to $\alpha_4\beta_1$ integrin. Compounds which bind in this assay can be used to assess VCAM-1 levels in biological samples by conventional assays (e.g., competitive binding assays). This assay is sensitive to IC_{50} values as low as about 1nM.

The activity of $\alpha_4\beta_1$ integrin was measured by the interaction of soluble VCAM-1 with Jurkat cells (e.g., American Type Culture Collection Nos. TIB 152, TIB 153, and CRL 8163), a human T-cell line which expresses high levels of $\alpha_4\beta_1$ integrin. VCAM-1 interacts with the cell surface in an $\alpha_4\beta_1$ integrin-dependent fashion (Yednock, et al. J. Biol. Chem., 1995, 270:28740).

Recombinant soluble VCAM-1 was expressed as a chimeric fusion protein containing the seven extracellular domains of VCAM-1 on the N-terminus and the human IgG_1 heavy chain constant region on the C-terminus. The VCAM-1 fusion protein was made and purified by the manner described by Yednock, *supra*.

Jurkat cells were grown in RPMI 1640 supplemented with 10% fetal bovine serum, penicillin, streptomycin and glutamine as described by Yednock, *supra*.

Jurkat cells were incubated with 1.5 mM $MnCl_2$ and 5 μg/mL 15/7 antibody for 30 minutes on ice. Mn^{+2} activates the receptor to enhance ligand binding, and 15/7 is a monoclonal antibody that recognizes an activated/ligand occupied conformation of $\alpha_4\beta_1$ integrin and locks the

molecule into this conformation thereby stabilizing the VCAM-1/$\alpha_4\beta_1$ integrin interaction. Yednock, et al., *supra*. Antibodies similar to the 15/7 antibody have been prepared by other investigators (Luque, et al, 1996, J. Biol. Chem. 271:11067) and may be used in this assay.

Cells were then incubated for 30 minutes at room temperature with candidate compounds, in various concentrations ranging from 66 μM to 0.01 μM using a standard 5-point serial dilution. 15 μL soluble recombinant VCAM-1 fusion protein was then added to Jurkat cells and incubated for 30 minutes on ice. (Yednock et al., *supra.*).

Cells were then washed two times and resuspended in PE-conjugated goat F(ab')$_2$ anti-mouse IgG Fc (Immunotech, Westbrook, ME) at 1:200 and incubated on ice, in the dark, for 30 minutes. Cells were washed twice and analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock, et al., *supra*.

Compounds having an IC_{50} of less than about 15μM possess binding affinity to $\alpha_4\beta_1$.

When tested in this assay, each of the compounds in Examples 1-45 has an IC_{50} of 15 μM or less.

Example 47

In vitro Saturation Assay For Determining Binding of Candidate Compounds to $\alpha_4\beta_1$

The following describes an *in vitro* assay to determine the plasma levels needed for a compound to be active in the Experimental Autoimmune

Encephalomyelitis ("EAE") model, described in the next example, or in other *in vivo* models.

Log-growth Jurkat cells are washed and resuspended in normal animal plasma containing 20 μg/ml of the 15/7 antibody (described in the above example).

The Jurkat cells are diluted two-fold into either normal plasma samples containing known candidate compound amounts in various concentrations ranging from 66 μM to 0.01 μM, using a standard 12 point serial dilution for a standard curve, or into plasma samples obtained from the peripheral blood of candidate compound-treated animals.

Cells are then incubated for 30 minutes at room temperature, washed twice with phosphate-buffered saline ("PBS") containing 2% fetal bovine serum and 1mM each of calcium chloride and magnesium chloride (assay medium) to remove unbound 15/7 antibody.

The cells are then exposed to phycoerythrin-conjugated goat F(ab')$_2$ anti-mouse IgG Fc (Immunotech, Westbrook, ME), which has been adsorbed for any non-specific cross-reactivity by co-incubation with 5% serum from the animal species being studied, at 1:200 and incubated in the dark at 4°C for 30 minutes.

Cells are washed twice with assay medium and resuspended in the same. They are then analyzed with a standard fluorescence activated cell sorter ("FACS") analysis as described in Yednock et al. J. Biol. Chem., 1995, 270:28740.

The data is then graphed as fluorescence versus dose, e.g., in a normal dose-response fashion. The dose levels that result in the upper plateau of the curve represent the levels needed to obtain efficacy in an *in vivo* model.

This assay may also be used to determine the plasma levels needed to saturate the binding sites of other integrins, such as the $\alpha_9\beta_1$ integrin, which is the integrin most closely related $\alpha_4\beta_1$ (Palmer et al, 1993, J. Cell Bio., 123:1289). Such binding is predictive of *in vivo* utility for inflammatory conditions mediated by $\alpha_9\beta_1$ integrin, including by way of example, airway hyper-responsiveness and occlusion that occurs with chronic asthma, smooth muscle cell proliferation in atherosclerosis, vascular occlusion following angioplasty, fibrosis and glomerular scarring as a result of renal disease, aortic stenosis, hypertrophy of synovial membranes in rheumatoid arthritis, and inflammation and scarring that occur with the progression of ulcerative colitis and Crohn's disease.

Accordingly, the above-described assay may be performed with a human colon carcinoma cell line, SW 480 (ATTC #CCL228) transfected with cDNA encoding α_9 integrin (Yokosaki et al., 1994, J. Biol. Chem., 269:26691), in place of the Jurkat cells, to measure the binding of the $\alpha_9\beta_1$ integrin. As a control, SW 480 cells which express other α and β_1 subunits may be used.

Accordingly, another aspect of this invention is directed to a method for treating a disease in a mammalian patient, which disease is mediated by $\alpha_9\beta_1$, and which method comprises administering to said patient a therapeutically effective amount of a compound of this invention. Such compounds are preferably administered in a pharmaceutical composition described herein above. Effective daily dosing will depend upon the age, weight, condition of the patient which factors can be readily ascertained by

the attending clinician. However, in a preferred embodiment, the compounds are administered from about 20 to 500 μg/kg per day. Using a conventional oral formulation, compounds of this invention would be active in this model.

Example 48

***In vivo* Evaluation**

The standard multiple sclerosis model, Experimental Autoimmune (or Allergic) Encephalomyelitis ("EAE"), is used to determine the effect of candidate compounds to reduce motor impairment in rats or guinea pigs. Reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory activity in the candidate compound. This model has been previously described by Keszthelyi et al., Neurology, 1996, 47:1053-1059, and measures the delay of onset of disease.

Brains and spinal cords of adult Hartley guinea pigs are homogenized in an equal volume of phosphate-buffered saline. An equal volume of Freund's complete adjuvant (100 mg *mycobacterium tuberculosis* plus 10 ml Freund's incomplete adjuvant) is added to the homogenate. The mixture is emulsified by circulating it repeatedly through a 20 ml syringe with a peristaltic pump for about 20 minutes.

Female Lewis rats (2-3 months old, 170-220 g) or Hartley guinea pigs (20 day old, 180-200 g) are anesthetized with isoflurane and three injections of the emulsion, 0.1 ml each, are made in each flank. Motor impairment onset is seen in approximately 9 days.

Candidate compound treatment begins on Day 8, just before onset of symptoms. Compounds are administered subcutaneously ("SC"), orally ("PO") or intraperitoneally ("IP"). Doses are given in a range of 10mg/kg to 200 mg/kg, bid, for five days, with typical dosing of 10 to 100 mg/kg SC, 10 to 50 mg/kg PO, and 10 to 100 mg/kg IP.

Antibody GG5/3 against $\alpha_4\beta_1$ integrin (Keszthelyi et al., Neurology, 1996, 47:1053-1059), which delays the onset of symptoms, is used as a positive control and is injected subcutaneously at 3 mg/kg on Day 8 and 11.

Body weight and motor impairment are measured daily. Motor impairment is rated with the following clinical score:

0	no change
1	tail weakness or paralysis
2	hindlimb weakness
3	hindlimb paralysis
4	moribund or dead

A candidate compound is considered active if it delays the onset of symptoms, e.g., produces clinical scores no greater than 2 or slows body weight loss as compared to the control.

Example 49

Asthma Model

Inflammatory conditions mediated by $\alpha_4\beta_1$ integrin include, for example, airway hyper-responsiveness and occlusion that occurs with chronic asthma. The following describes an asthma model which can be

used to study the *in vivo* effects of the compounds of this invention for use in treating asthma.

Following the procedures described by Abraham et al, J. Clin. Invest, 93:776-787 (1994) and Abraham et al, Am J. Respir Crit Care Med, 156:696-703 (1997), both of which are incorporated by reference in their entirety, compounds of this invention are formulated into an aerosol and administered to sheep which are hypersensitive to *Ascaris suum* antigen. Compounds which decrease the early antigen-induced bronchial response and/or block the late-phase airway response, e.g., have a protective effect against antigen-induced late responses and airway hyper-responsiveness ("AHR"), are considered to be active in this model.

Allergic sheep which are shown to develop both early and late bronchial responses to inhaled *Ascaris suum* antigen are used to study the airway effects of the candidate compounds. Following topical anesthesia of the nasal passages with 2% lidocaine, a balloon catheter is advanced through one nostril into the lower esophagus. The animals are then intubated with a cuffed endotracheal tube through the other nostril with a flexible fiberoptic bronchoscope as a guide.

Pleural pressure is estimated according to Abraham (1994). Aerosols (see formulation below) are generated using a disposable medical nebulizer that provides an aerosol with a mass median aerodynamic diameter of 3.2 μm as determined with an Andersen cascade impactor. The nebulizer is connected to a dosimeter system consisting of a solenoid valve and a source of compressed air (20 psi). The output of the nebulizer is directed into a plastic T-piece, one end of which is connected to the inspiratory port of a piston respirator. The solenoid valve is activated for 1 second at the beginning of the inspiratory cycle of the respirator. Aerosols are delivered

at V_T of 500 ml and a rate of 20 breaths/minute. A 0.5% sodium bicarbonate solution only is used as a control.

To assess bronchial responsiveness, cumulative concentration-response curves to carbachol can be generated according to Abraham (1994). Bronchial biopsies can be taken prior to and following the initiation of treatment and 24 hours after antigen challenge. Bronchial biopsies can be preformed according to Abraham (1994).

An *in vitro* adhesion study of alveolar macrophages can be performed according to Abraham (1994), and a percentage of adherent cells is calculated.

Aerosol Formulation

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

A. Preparation of 0.5% Sodium Bicarbonate/Saline Stock Solution: 100.0 mL

Ingredient	Gram / 100.0 mL	Final Concentration
Sodium Bicarbonate	0.5 g	0.5%
Saline	q.s. ad 100.0 mL	q.s. ad 100%

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL

Ingredient	Gram / 10.0 mL	Final Concentration
Candidate Compound	0.300 g	30.0 mg/mL
0.5% Sodium Bicarbonate / Saline Stock Solution	q.s. ad 10.0 mL	q.s ad 100%

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.

2. Add approximately 9.7 mL of 0.5% sodium bicarbonate / saline stock solution.

3. Sonicate until the candidate compound is completely dissolved.

4. Q.S. to 10.0 mL with 0.5% sodium bicarbonate / saline stock solution and mix thoroughly.

Using a conventional oral formulation, compounds of this invention would be active in this model.

WHAT IS CLAIMED IS:

1. A compound of formula I:

$$
\begin{array}{c}
\qquad\qquad\qquad R^3 \qquad\quad O \\
\qquad\qquad\qquad | \qquad\quad \| \\
R^1\text{-}SO_2\text{-}N(R^2)\text{-}C\text{-}Q\text{-}CH\text{-}C\text{-}OH \\
\qquad\qquad | \qquad | \\
\qquad\qquad H \qquad R^5
\end{array}
\qquad\qquad \mathrm{I}
$$

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, and where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form an unsaturated heterocyclic group or a unsaturated substituted heterocyclic group;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur; and

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic,

with the further provisos that:

A. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-O-Z-NR^8R^{8'}$ and $-O-Z-R^{12}$ wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

B. R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{12}C(Z')NR^8R^{8'}$ and $-NR^{12}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{12}, R^{12} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is sustituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than

morpholino and thiomorpholino, substituted heterocyclic or R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur, at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,

x is an integer of from 1 to 4;

C. R^5 is not -ALK-X' where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group ($-CH_2-$) to the carbon atom to which it is attached; X' is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroaryloxycarbonyl, substituted heteroaryloxycarbonyl, heterocyclyloxycarbonyl, substituted heterocyclyloxycarbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocarbonylamino, guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-cycloalkyl, $-OS(O)_2$-substituted cycloalkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl,

$-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-cycloalkyl, $-NRS(O)_2$-substituted cycloalkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-cycloalkyl, $-NRS(O)_2$-NR-substituted cycloalkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, $-S(O)_2$-alkyl, $-S(O)_2$-substituted alkyl, $-S(O)_2$-aryl, $-S(O)_2$-substituted aryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-substituted heteroaryl, $-S(O)_2$-heterocyclic, $-S(O)_2$-substituted heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-(substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl, substituted heterocyclic)amino;

D. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is a substituent selected from the group consisting of:

(a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino,

thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heterarylоxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic,

substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and $-COOR^{23}$ where R^{23} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic,

(c) aryl and heteroaryl;

(d) -NR'R' wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy,

substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, -SO_2-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(e) -alkoxy-NR″R″ wherein each R″ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when each R″ is substituted alkyl then at least one of the substituents on the substituted

alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl,

substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-alkenyl, -SO_2-substituted alkenyl, -SO_2-cycloalkyl, -SO_2-substituted cycloalkyl, -SO_2-aryl, -SO_2-substituted aryl, -SO_2-heteroaryl, -SO_2-substituted heteroaryl, -SO_2-heterocyclic, -SO_2-substituted heterocyclic or -SO_2NRR, where R is hydrogen or alkyl;

(f) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(g) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic;

(h) -O-heterocyclic and -O-substituted heterocyclic;

(i) tetrazolyl;

(j) -NR-SO_2-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(k) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

(l) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR"R", unsaturated heterocyclyl, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(m) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(n) -C(O)NR'''R''' where each R''' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R''' is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic and substituted heterocyclic;

(o) -NR^{22}C(O)-R^{18} where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted

aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(p) $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl or $-SO_2$-alkyl;

(q) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic:

(r) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) -aminocarbonyl-(N-formylheterocylcyl); and

(t) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl, and

E. When R^3 is other than H, R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl then at least one of the substituents on the

substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heterayloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl,

substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof

and still further with the following provisos excluding the following compounds

A. when R^1 and R^2 are joined together with the SO_2 and nitrogen atom to which they are attached respectively to form a benzoisothiazolone heterocyclic ring, R^3 is hydrogen, and Q is -C(O)NH-, then R^5 is not benzyl; and

B. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 is hydrogen, Q is $-C(O)NCH_3-$, then R^5 is not benzyl.

2. A compound of formula IA:

$$\begin{array}{c} \qquad\qquad\qquad\quad R^3 \qquad\quad O \\ \qquad\qquad\qquad\quad | \qquad\quad \| \\ R^1\text{-}SO_2\text{-}N(R^2)\text{-}C\text{-}Q\text{-}CH\text{-}C\text{-}R^6 \\ \qquad\qquad\qquad\quad | \qquad | \\ \qquad\qquad\qquad\quad H \qquad R^6 \end{array} \qquad \text{IA}$$

where

R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl;

R^2 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted

cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form an unsaturated heterocyclic group or a unsaturated substituted heterocyclic group;

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), amino, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, -O-(N-succinimidyl), -NH-adamantyl, -O-cholest-5-en-3-β-yl, -NHOY where Y is hydrogen, alkyl, substituted alkyl, aryl, and substituted aryl, $-NH(CH_2)_pCOOY$ where p is an integer of from 1 to 8 and Y is as defined above, $-OCH_2NR^9R^{10}$ where R^9 is selected from the group consisting of -C(O)-aryl and -C(O)-substituted aryl and R^{10} is selected from the group consisting of hydrogen and $-CH_2COOR^{11}$ where R^{11} is alkyl, and $-NHSO_2Z''$ where Z'' is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl;

X is selected from the group consisting of oxygen and sulfur;

R^5 is $-CH_2X$ where X is selected from the group consisting of hydrogen, hydroxyl, acylamino, alkyl, alkoxy, aryloxy, aryl, aryloxyaryl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl,

carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted alkyl, substituted alkoxy, substituted aryl, substituted aryloxy, substituted aryloxyaryl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic,

with the further provisos that:

A. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

Ar is aryl, heteroaryl, substituted aryl or substituted heteroaryl,

x is an integer of from 1 to 4;

B. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{12}C(Z')NR^8R^{8'}$ and $-NR^{12}C(Z')R^{13}$ wherein Z' is selected from the group consisting of oxygen, sulfur and NR^{12}, R^{12} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z' is oxygen, at least one of R^8 and $R^{8'}$ is sustituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, substituted heterocyclic or R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z' is sulfur,

at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, and R^{13} is selected from the group consisting of substituted heterocycles and saturated heterocycles other than morpholino and thiomorpholino,

Ar is aryl, substituted aryl, heteroaryl or substituted heteroaryl,

x is an integer of from 1 to 4;

C. R^5 is not -ALK-X' where ALK is an alkyl group of from 1 to 10 carbon atoms attached via a methylene group ($-CH_2-$) to the carbon atom to which it is attached; X' is selected from the group consisting of substituted alkylcarbonylamino, substituted alkenylcarbonylamino, substituted alkynylcarbonylamino, heterocyclylcarbonylamino, substituted heterocyclylcarbonylamino, acyl, acyloxy, aminocarbonyloxy, acylamino, oxycarbonylamino, alkoxycarbonyl, substituted alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, cycloalkoxycarbonyl, substituted cycloalkoxycarbonyl, heteroaryloxycarbonyl, substituted heteroaryloxycarbonyl, heterocyclyloxycarbonyl, substituted heterocyclyloxycarbonyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic, substituted saturated heterocyclic, substituted alkoxy, substituted alkenoxy, substituted alkynoxy, heterocyclyloxy, substituted heterocycloxy, substituted thioalkyl, substituted thioalkenyl, substituted thioalkynyl, aminocarbonylamino, aminothiocarbonylamino, guanidino, amidino, alkylamidino, thioamidino, halogen, cyano, nitro, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-cycloalkyl, $-OS(O)_2$-substituted cycloalkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR where R is hydrogen or alky, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-cycloalkyl, $-NRS(O)_2$-substituted cycloalkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-

substituted alkyl, -NRS(O)$_2$-NR-cycloalkyl, -NRS(O)$_2$-NR-substituted cycloalkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic where R is hydrogen or alkyl, -S(O)$_2$-alkyl, -S(O)$_2$-substituted alkyl, -S(O)$_2$-aryl, -S(O)$_2$-substituted aryl, -S(O)$_2$-substituted heteroaryl, -S(O)$_2$-substituted heteroaryl, -S(O)$_2$-heterocyclic, -S(O)$_2$-substituted heterocyclic, mono- and di-(substituted alkyl)amino, N,N-(alkyl, substituted alkyl)amino, N,N-(aryl, substituted alkyl)amino, N,N-(substituted aryl, substituted alkyl)amino, N,N-(heteroaryl, substituted alkyl)amino, N,N-(substituted heteroaryl, substituted alkyl)amino, N,N-(heterocyclic, substituted alkyl)amino, N,N-N,N-(substituted heterocyclic, substituted alkyl)amino, mono- and di-(heterocyclic)amino, mono- and di-(substituted heterocyclic)amino, N,N-(alkyl, heterocyclic)amino, N,N-(alkyl, substituted heterocyclic)amino, N,N-(aryl, heterocyclic)amino, N,N-(substituted aryl, heterocyclic)amino, N,N-(aryl, substituted heterocyclic)amino, N,N-(substituted aryl, substituted heterocyclic)amino, N,N-(heteroaryl, heterocyclic)amino, N,N-(heteroaryl, substituted heterocyclic)amino, N,N-(substituted heteroaryl, heterocyclic)amino, and N,N-(substituted heteroaryl, substituted heterocyclic)amino;

D. R^5 is not -(CH$_2$)$_x$-Ar-$R^{5'}$ where $R^{5'}$ is a substituent selected from the group consisting of:

(a) substituted alkylcarbonylamino with the proviso that at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-

substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, -

SO_2-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(b) alkoxyaryl substituted on the alkoxy moiety with a substituent selected from the group consisting of carboxyl and $-COOR^{23}$ where R^{23} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl or heterocyclic,

(c) aryl and heteroaryl;

(d) $-NR'R'$ wherein each R' is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic with the proviso that at least one of R' is substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic and substituted heterocyclic and with the further proviso that when R' is substituted alkyl at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted

heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, $-NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, $-NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, $-NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(e) -alkoxy-NR″R″ wherein each R″ is independently selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when each R″ is substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy, aryloxy, substituted aryloxy,

cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heteraryloxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, -OS(O)$_2$-alkyl, -OS(O)$_2$-substituted alkyl, -OS(O)$_2$-aryl, -OS(O)$_2$-substituted aryl, -OS(O)$_2$-heteroaryl, -OS(O)$_2$-substituted heteroaryl, -OS(O)$_2$-heterocyclic, -OS(O)$_2$-substituted heterocyclic, -OSO$_2$-NRR, -NRS(O)$_2$-alkyl, -NRS(O)$_2$-substituted alkyl, -NRS(O)$_2$-aryl, -NRS(O)$_2$-substituted aryl, -NRS(O)$_2$-heteroaryl, -NRS(O)$_2$-substituted heteroaryl, -NRS(O)$_2$-heterocyclic, -NRS(O)$_2$-substituted heterocyclic, -NRS(O)$_2$-NR-alkyl, -NRS(O)$_2$-NR-substituted alkyl, -NRS(O)$_2$-NR-aryl, -NRS(O)$_2$-NR-substituted aryl, -NRS(O)$_2$-NR-heteroaryl, -NRS(O)$_2$-NR-substituted heteroaryl, -NRS(O)$_2$-NR-heterocyclic, -NRS(O)$_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups and alkyl/substituted alkyl groups substituted with -SO$_2$-alkyl, -SO$_2$-substituted

alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

(f) substituted aryloxy and substituted heteroaryloxy with the proviso that at least one substituent on the substituted aryloxy/heteroaryloxy is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(g) -alkoxy-saturated heterocyclic, -alkoxy-saturated substituted heterocyclic, -substituted alkoxy-heterocyclic and -substituted alkoxy-substituted saturated heterocyclic;

(h) -O-heterocyclic and -O-substituted heterocyclic;

(i) tetrazolyl;

(j) $-NR-SO_2$-substituted alkyl where R is hydrogen, alkyl or aryl, with the proviso that at least one substituent on the alkyl moiety of the substituted alkylsulfonylamino is other than halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(k) alkenylsulfonylamino, alkynylsulfonylamino, substituted alkenylsulfonylamino and substituted alkynylsulfonylamino;

(l) substituted alkoxy with the proviso that the substitution on the alkyl moiety of said substituted alkoxy does not include alkoxy-NR"R", unsaturated heterocyclyl, alkyloxy, aryloxy, heteroaryloxy, aryl, heteroaryl and aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro,

trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea;

(m) amidine and amidine substituted with from 1 to 3 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic;

(n) -C(O)NR'''R''' where each R''' is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic with the proviso that when one R''' is unsaturated heterocyclic, aryl, heteroaryl or aryl/heteroaryl substituted with halogen, hydroxyl, amino, nitro, trifluoromethyl, trifluoromethoxy, alkyl, alkenyl, alkynyl, 1,2-dioxymethylene, 1,2-dioxyethylene, alkoxy, alkenoxy, alkynoxy, alkylamino, alkenylamino, alkynylamino, alkylcarbonyloxy, acyl, alkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, N-alkyl or N,N-dialkylurea, then the other R''' is alkyl, substituted alkyl (other than unsaturated heterocyclyl substituted-alkyl), cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, heterocyclic and substituted heterocyclic;

(o) -NR^{22}C(O)-R^{18} where R^{18} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{22} is alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic;

(p) $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl or $-SO_2$-alkyl;

(q) $-NR'C(O)NR^{19}R^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic and each R^{19} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic:

(r) $-NR'C(O)OR^{19}$ wherein R' is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic, and R^{19} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic;

(s) -aminocarbonyl-(N-formylheterocylcyl); and

(t) -alkyl-C(O)NH-heterocyclyl and -alkyl-C(O)NH-substituted heterocyclyl, and

E. When R^3 is other than H, R^5 is not $-(CH_2)_x-Ar-R^{5'}$ where $R^{5'}$ is substituted alkenyl or substituted alkynyl with the proviso that at least one of the substituents on the substituted alkenyl/alkynyl moiety is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic with the proviso that when substituted with substituted alkyl then at least one of the substituents on the substituted alkyl moiety is selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, thiocarbonylamino, acyloxy, alkenyl, amino, amidino, alkyl amidino, thioamidino, aminoacyl, aminocarbonylamino, aminothiocarbonylamino, aminocarbonyloxy,

aryloxy, substituted aryloxy, cyano, nitro, halogen, hydroxyl, carboxyl, carboxylalkyl, carboxyl-substituted alkyl, carboxyl-cycloalkyl, carboxyl-substituted cycloalkyl, carboxylaryl, carboxyl-substituted aryl, carboxylheteroaryl, carboxyl-substituted heteroaryl, carboxylheterocyclic, carboxyl-substituted heterocyclic, cycloalkyl, substituted cycloalkyl, guanidino, guanidinosulfone, thiol, thioalkyl, substituted thioalkyl, thioaryl, substituted thioaryl, thiocycloalkyl, substituted thiocycloalkyl, thioheteroaryl, substituted thioheteroaryl, thioheterocyclic, substituted thioheterocyclic, heterocyclic, substituted heterocyclic, cycloalkoxy, substituted cycloalkyoxy, heterarylоxy, substituted heteroaryloxy, heterocyclyloxy, substituted heterocyclyloxy, oxycarbonylamino, oxythiocarbonylamino, $-OS(O)_2$-alkyl, $-OS(O)_2$-substituted alkyl, $-OS(O)_2$-aryl, $-OS(O)_2$-substituted aryl, $-OS(O)_2$-heteroaryl, $-OS(O)_2$-substituted heteroaryl, $-OS(O)_2$-heterocyclic, $-OS(O)_2$-substituted heterocyclic, $-OSO_2$-NRR, $-NRS(O)_2$-alkyl, $-NRS(O)_2$-substituted alkyl, $-NRS(O)_2$-aryl, -$NRS(O)_2$-substituted aryl, $-NRS(O)_2$-heteroaryl, $-NRS(O)_2$-substituted heteroaryl, $-NRS(O)_2$-heterocyclic, $-NRS(O)_2$-substituted heterocyclic, -$NRS(O)_2$-NR-alkyl, $-NRS(O)_2$-NR-substituted alkyl, $-NRS(O)_2$-NR-aryl, -$NRS(O)_2$-NR-substituted aryl, $-NRS(O)_2$-NR-heteroaryl, $-NRS(O)_2$-NR-substituted heteroaryl, $-NRS(O)_2$-NR-heterocyclic, $-NRS(O)_2$-NR-substituted heterocyclic, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-(substituted aryl)amino, mono- and di-heteroarylamino, mono- and di-(substituted heteroaryl)amino, mono- and di-heterocyclic amino, mono- and di-(substituted heterocyclic) amino, and unsymmetric di-substituted amines having different substituents selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, substituted alkyl groups having amino groups blocked by conventional blocking groups (such as Boc, Cbz, formyl, and the like) and alkyl/substituted alkyl groups substituted with

$-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-cycloalkyl, $-SO_2$-substituted cycloalkyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, $-SO_2$-substituted heterocyclic or $-SO_2NRR$, where R is hydrogen or alkyl;

and pharmaceutically acceptable salts thereof,

with the following provisos

A. when R^1 is *o*-carboxymethylphenyl, R^2 is hydrogen, R^3 is hydrogen or methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

B. when R^1 and R^2 are joined to form a benzoisothiazolone heterocyclic ring, R^3 is hydrogen or methyl, R^5 is benzyl and Q is -C(O)NH-, then R^6 is not -O-benzyl;

C. when R^1 is *p*-methylphenyl, R^2 is hydrogen, R^5 is benzyl or *p*-hydroxybenzyl, R^3 is $-(CH_2)_sC(O)O$-*t*-butyl where *s* is 1 or 2, Q is -C(O)NH-, then R^6 is not -O-*t*-butyl;

D. when R^1 is *p*-methylphenyl, R^2 is methyl, R^5 is benzyl, R^3 is $-CH(\phi)_2$, Q is -C(O)NH-, then R^6 is not -O-benzyl;

E. when R^1 is *p*-methylphenyl, R^2 is methyl, R^5 is methyl, R^3 is -hydroxymethyl, Q is -C(O)NH-, then R^6 is not -O-methyl; and

F. when R^1 is *p*-methylphenyl, R^2 is methyl, R^3 is methyl or *t*-butyl, R^5 is *p*-hydroxybenzyl, Q is -C(O)NH-, then R^6 is not -O-*t*-butyl.

3. A compound according to Claims 1 or 2 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

4. A compound according to Claims 1 or 2 wherein R^1 is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-

dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3′-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

5. A compound according to Claims 1 or 2 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-ϕ.

6. A compound according to Claims 1 or 2 wherein R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 are joined to form a heterocyclic group or substituted heterocyclic group.

7. A compound according to Claims 1 or 2 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylmethyl, -CH_2CH_2-COOH, -CH_2-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH_2O-benzyl and hydroxymethyl.

8. A compound according to Claims 1 or 2 wherein R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 are joined to form an unsaturated heterocyclic group or an unsaturated substituted heterocyclic group.

9. A compound according to Claims 1 or 2 wherein Q is -C(O)NH- or -C(S)NH-.

10. A compound according to Claims 1 or 2 wherein R^5 is selected from the group consisting of benzyl, (*N*-benzylimidazol-4-yl)methyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, 4-[2-(pyridin-2-yl)ethynyl]benzyl, 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-iodobenzyl, 4-cyanobenzyl, 4-(2-bromobenzamido)benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, and 4-hydroxybenzyl.

11. A compound according to Claims 1 or 2 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2-α-*iso*-propyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, $-NH_2$, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHCH_2CH_2COOCH_2CH_3$, $-NHSO_2$-*p*-CH_3-ϕ, $-NHOR^8$ where R^8 is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, $-OCH_2-OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where *z* is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR″C(O)-R′ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or $-CH_2C(O)OCH_2CH_3$.

12. A compound selected from the group consisting of

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-phenylalanine

N-(toluene-4-sulfonyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)glycyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)-L-alanyl-L-phenylalanine

N-(saccharin-2-yl)-L-alanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-phenylalanyl-D,L-phenylalanine

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(3-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(4-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-L-β-(2-pyridyl)alanine

N-(toluene-4-sulfonyl)-D,L-phenylsarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-aspartyl-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinolin-3-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(pyridin-2-yl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(3-hydroxyphenyl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-(iodo)phenylalanine

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-cyanophenylalanine

N-(toluene-4-sulfonyl)-L-*tert*-butylglycyl-L-phenylalanine

N-(saccharin-2-yl)-D,L-alaninyl-L-4-(isonicotinamido)phenylalanine methyl ester

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

13. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of Claims 1 or 2 under conditions wherein said compound binds to VLA-4.

14. The method of claim 13 wherein R^1 is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic, substituted heterocylic, heteroaryl and substituted heteroaryl.

15. The method of claim 13 wherein R^1 is selected from the group consisting of 4-methylphenyl, methyl, benzyl, *n*-butyl, 4-chlorophenyl, 1-naphthyl, 2-naphthyl, 4-methoxyphenyl, phenyl, 2,4,6-trimethylphenyl, 2-(methoxycarbonyl)phenyl, 2-carboxyphenyl, 3,5-dichlorophenyl, 4-trifluoromethylphenyl, 3,4-dichlorophenyl, 3,4-dimethoxyphenyl, 4-($CH_3C(O)NH$-)phenyl, 4-trifluoromethoxyphenyl, 4-cyanophenyl, isopropyl, 3,5-di-(trifluoromethyl)phenyl, 4-*t*-butylphenyl, 4-*t*-butoxyphenyl, 4-nitrophenyl, 2-thienyl, 1-N-methyl-3-methyl-5-chloropyrazol-4-yl, phenethyl, 1-N-methylimidazol-4-yl, 4-bromophenyl, 4-amidinophenyl, 4-methylamidinophenyl, 4-[$CH_3SC(=NH)$]phenyl, 5-

chloro-2-thienyl, 2,5-dichloro-4-thienyl, 1-N-methyl-4-pyrazolyl, 2-thiazolyl, 5-methyl-1,3,4-thiadiazol-2-yl, 4-[$H_2NC(S)$]phenyl, 4-aminophenyl, 4-fluorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, pyridin-3-yl, pyrimidin-2-yl, 4-(3'-dimethylamino-*n*-propoxy)-phenyl, and 1-methylpyrazol-4-yl.

16. The method of claim 13 wherein R^2 is selected from the group consisting of hydrogen, methyl, phenyl, benzyl, -$(CH_2)_2$-2-thienyl, and -$(CH_2)_2$-ϕ.

17. The method of claim 13 wherein R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 are joined to form a heterocyclic group or substituted heterocyclic group.

18. The method of claim 13 wherein R^3 is selected from the group consisting of methyl, phenyl, benzyl, diphenylmethyl, -CH_2CH_2-COOH, -CH_2-COOH, 2-amidoethyl, *iso*-butyl, *t*-butyl, -CH_2O-benzyl and hydroxymethyl.

19. The method of claim 13 wherein R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 are joined to form an unsaturated heterocyclic group or an unsaturated substituted heterocyclic group.

20. The method of claim 13 wherein Q is -C(O)NH- or -C(S)NH-.

21. The method of claim 13 wherein R^5 is selected from the group consisting of benzyl, (*N*-benzylimidazol-4-yl)methyl, (pyridin-2-yl)methyl, (pyridin-3-yl)methyl, (pyridin-4-yl)methyl, 4-[2-(pyridin-2-yl)ethynyl]benzyl, 4-[2-(3-hydroxyphenyl)ethynyl]benzyl, 4-iodobenzyl, 4-

cyanobenzyl, 4-(2-bromobenzamido)benzyl, 4-(pyridin-4-yl-C(O)NH-)benzyl, and 4-hydroxybenzyl.

22. The method of claim 13 wherein R^6 is selected from the group consisting of 2,4-dioxo-tetrahydrofuran-3-yl (3,4-enol), methoxy, ethoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, cyclopentoxy, *neo*-pentoxy, 2-α-*iso*-propyl-4-β-methylcyclohexoxy, 2-β-isopropyl-4-β-methylcyclohexoxy, $-NH_2$, benzyloxy, $-NHCH_2COOH$, $-NHCH_2CH_2COOH$, -NH-adamantyl, $-NHCH_2CH_2COOCH_2CH_3$, $-NHSO_2$-*p*-CH_3-ϕ, $-NHOR^8$ where R^8 is hydrogen, methyl, *iso*-propyl or benzyl, O-(N-succinimidyl), -O-cholest-5-en-3-β-yl, $-OCH_2-OC(O)C(CH_3)_3$, $-O(CH_2)_zNHC(O)W$ where z is 1 or 2 and W is selected from the group consisting of pyrid-3-yl, N-methylpyridyl, and N-methyl-1,4-dihydro-pyrid-3-yl, -NR″C(O)-R′ where R′ is aryl, heteroaryl or heterocyclic and R″ is hydrogen or $-CH_2C(O)OCH_2CH_3$.

23. The method of claim 13 wherein the compound is selected from the group consisting of:

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-phenylalanine

N-(toluene-4-sulfonyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)glycyl-L-phenylalanine

N-(2-methoxycarbonylbenzenesulfonyl)-L-alanyl-L-phenylalanine

N-(saccharin-2-yl)-L-alanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-phenylalanyl-D,L-phenylalanine

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-diphenylalanyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(3-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-β-(4-pyridyl)alanine

N-(toluene-4-sulfonyl)sarcosyl-L-β-(2-pyridyl)alanine

N-(toluene-4-sulfonyl)-D,L-phenylsarcosyl-L-phenylalanine

N-(toluene-4-sulfonyl)-L-aspartyl-L-phenylalanine

N-(toluene-4-sulfonyl)-(2S-1,2,3,4-tetrahydroisoquinolin-3-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-(2S-indolin-2-carbonyl)-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-L-alanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-(*O*-benzyl)seryl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)-L-diphenylalanyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-phenylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine ethyl ester

N-(toluene-4-sulfonyl)sarcosyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-methyl-D,L-phenylglycyl-L-phenylalanine benzyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-benzylglycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(pyridin-2-yl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-4-[2-(3-hydroxyphenyl)ethynyl]-D,L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-(iodo)phenylalanine

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-thienylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)-*N*-methyl-L-seryl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-(*N*-benzyl)histidine methyl ester

N-(toluene-4-sulfonyl)-*N*-(2-phenylethyl)glycyl-L-phenylalanine

N-(toluene-4-sulfonyl)sarcosyl-D,L-4-cyanophenylalanine

N-(toluene-4-sulfonyl)-L-*tert*-butylglycyl-L-phenylalanine

N-(saccharin-2-yl)-D,L-alaninyl-L-4-(isonicotinamido)phenylalanine methyl ester

and pharmaceutically acceptable salts thereof as well as any of the ester compounds recited above wherein one ester is replaced with another ester

selected from the group consisting of methyl ester, ethyl ester, *n*-propyl ester, isopropyl ester, *n*-butyl ester, isobutyl ester, *sec*-butyl ester and *tert*-butyl ester.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of Claims 1 or 2.

25. A method for treating an inflammatory disease in a mammalian patient which disease is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of the pharmaceutical composition of Claim 24.

26. The method according to Claim 25 wherein said inflammatory condition is selected from the group consisting of asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetis), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

INTERNATIONAL SEARCH REPORT

Inten   nal Application No
PCT/US 98/15952

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/062 C07K5/065 C07K5/072 C07K5/078 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22966 A (BIOGEN INC ;ADAMS STEVEN P (US); LIN KO CHUNG (US); LEE WEN CHERNG) 1 August 1996 see compound BIO1013 see page 46, line 32 - page 47, line 35; claims ---	1,2,13, 24-26
X	WO 94 07815 A (ABBOTT LAB) 14 April 1994 see page 3, line 5 - line 16; claims; example 105 ---	1
X	EP 0 526 348 A (SANOFI ELF) 3 February 1993 see claims; examples 33,62,66,69 --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 1998	12/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 98/15952

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 12181 A (MERCK & CO INC ;EGBERTSON MELISSA S (US); TURCHI LAURA M (US); HAR) 9 June 1994 see claims; example 31 ---	1,2
X	CHEMICAL ABSTRACTS, vol. 125, no. 3, 15 July 1996 Columbus, Ohio, US; abstract no. 34164, INOE, TOSHIHISA ET AL: "Preparation of amino acid esters and detection of leukocyte, esterase, or protease" XP002087653 see abstract -& JP 08 073422 A (KYOTO DAIICHI KAGAKU KK, JAPAN) see page 6 ---	1
A	WO 95 15973 A (CYTEL CORP) 15 June 1995 see page 8, line 16 - line 26; claims; examples -----	1,2,13, 24-26

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INTERNATIONAL SEARCH REPORT	International application No. PCT/US 98/ 15952

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 25 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ...nal Application No
PCT/US 98/15952

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